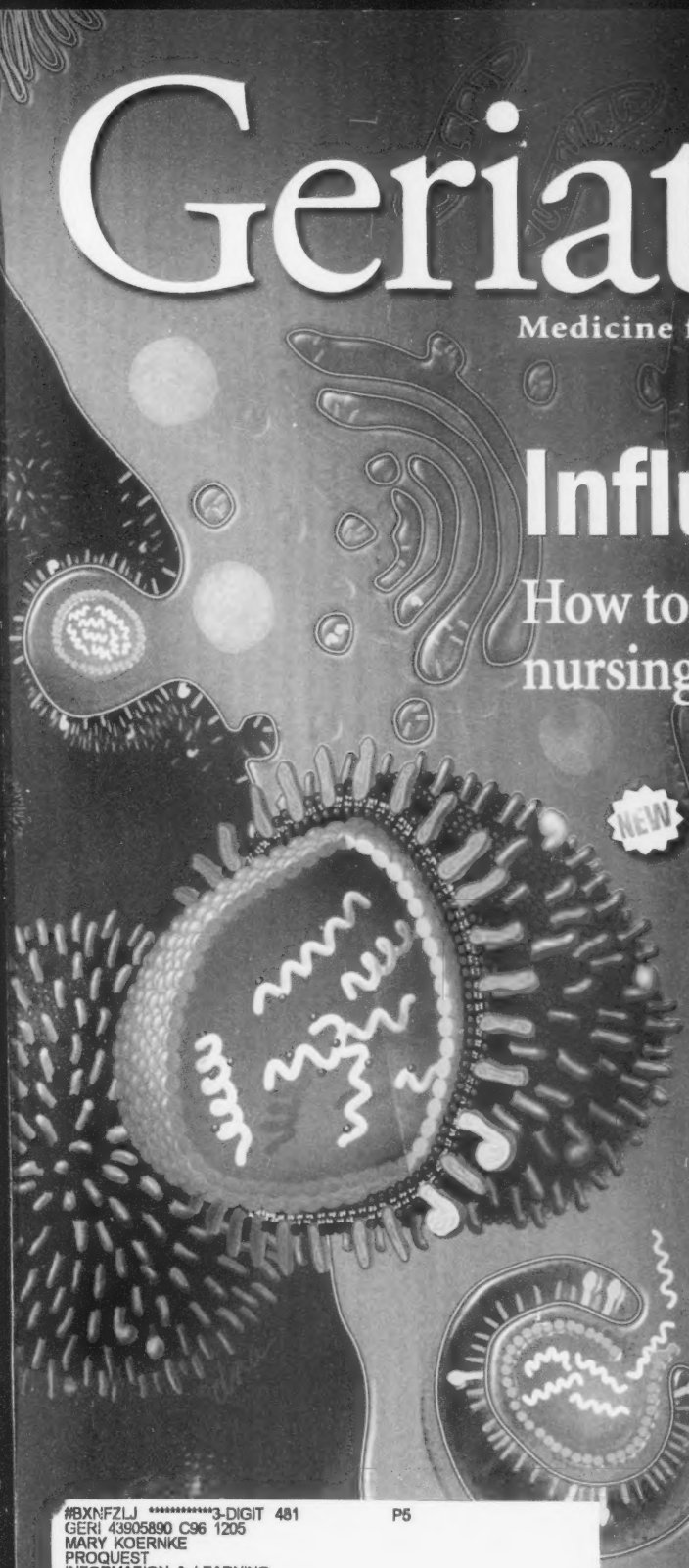
January 2002

Geriatrics®

Medicine for Midlife and Beyond



Influenza

How to prevent and control nursing home outbreaks

NEW **CME/ The Brain**
Stroke and TIA: Prevention and management in primary care practice

M·S SM

Editorial/Dr. Sherman
Can your patient eat? Bedside test provides food for thought

Psychiatric Consultant
Promoting mental health, treating mental illness

Abstracts from current literature

• Complete contents, pages 7 & 8

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AN ADVANSTAR ★ HEALTHCARE PUBLICATION

* *Individual responses to ARICEPT® may include improvement, stabilization, or decline.*

† The most common adverse events in pivotal clinical trials with ARICEPT® were nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia. Pivotal clinical trials of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. Nevertheless, cholinesterase inhibitors may be expected to increase gastric acid secretion. Therefore, patients (especially those at increased risk for developing ulcers—eg, having a history of ulcer disease, receiving concurrent nonsteroidal anti-inflammatory drugs) should be monitored closely for gastrointestinal bleeding. In pivotal clinical trials, syncopal episodes have been reported in association with ARICEPT® (2% vs 1% for placebo).

function.

She sees it as a bedtime story.

ARICEPT®. Helping to make a difference for people living with Alzheimer's

- Slows the worsening of symptoms*
- Proven to maintain cognition in placebo-controlled studies
- Well tolerated†
- Proven safety profile
- Once-daily dosing
- 3 years of real-world use

ONCE-A-DAY

ARICEPT®

(donepezil HCl)

5-MG AND 10-MG TABLETS

THERAPY TO REMEMBER™

Please see brief summary of prescribing information on adjacent page.

EL208A99CR

ARICEPT® (Donepezil Hydrochloride Tablets)

Brief Summary—see package insert for full prescribing information. **INDICATIONS AND USAGE** ARICEPT® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. **CONTRAINDICATIONS** ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS** ***Anesthesia:*** ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. ***Cardiovascular Conditions:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on the sinoatrial and atrioventricular nodes. This effect may manifest as bradycardia or heart attack in patients both with or without known underlying cardiac conduction abnormalities. Syncopal episodes have been reported in association with the use of ARICEPT®. ***Gastrointestinal Conditions:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®. ***Genitourinary:*** Although not observed in clinical trials of ARICEPT®,cholinomimetics may cause bladder outflow obstruction. ***Neurological Conditions:*** Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease. ***Pulmonary Conditions:*** Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **PRECAUTIONS Drug-Drug Interactions** ***Drugs Highly Bound to Plasma Proteins:*** Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. ARICEPT® at concentrations of 0.3-10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL), and warfarin (3 µg/mL) to human albumin. Similarly, the binding of ARICEPT® to human albumin was not affected by furosemide, digoxin, and warfarin. ***Effect of ARICEPT® on the Metabolism of Other Drugs:*** No *in vivo* clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_i about 50-130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT® has any potential for enzyme induction is not known. ***Effect of Other Drugs on the Metabolism of ARICEPT®:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of these inhibitors is not known. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of ARICEPT®. ***Use with Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. ***Use with Cholinomimetics and Other Cholinesterase Inhibitors:*** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity studies of donepezil have not been completed. Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis). **Pregnancy** ***Pregnancy Category C:*** Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m^2 basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m^2 basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose, the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers. **Pediatric Use** There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children. **ADVERSE REACTIONS Adverse Events Leading to Discontinuation** The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group

Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®
Patients Randomized	355	350	315
Event/%Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT® The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day. See Table 2 for a comparison of the most common adverse events following one and six week titration regimens.

Table 2. Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks

Adverse Event	Placebo (n=315)	No titration 5 mg/day (n=311)	One-week titration 10 mg/day (n=315)	Six-week titration 10 mg/day (n=269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Adverse Events Reported in Controlled Trials The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

Table 3. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT® (donepezil HCl) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=355)	ARICEPT® (n=747)
Percent of Patients with any Adverse Event	**72**	**74**
Body as a Whole		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular System		
Syncope	1	2
Digestive System		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and Lymphatic System		
Ecchymosis	3	4
Metabolic and Nutritional Systems		
Weight Decrease	1	3
Musculoskeletal System		
Muscle Cramps	2	6
Arthritis	1	2
Nervous System		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal Dreams	0	3
Somnolence	<1	2
Urogenital System		
Frequent Urination	1	2

Other Adverse Events Observed During Clinical Trials ARICEPT® has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days. Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT®. All adverse events occurring at least twice are included, except for those already listed in Tables 2 or 3, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events*—those occurring in at least 1/100 patients; *infrequent adverse events*—those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States. **Body as a Whole:** *Frequent:* influenza, chest pain, toothache; *Infrequent:* fever, edema face, periorbital edema, hernia hiatal, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness. **Cardiovascular System:** *Frequent:* hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; *Infrequent:* angina pectoris, postural hypotension, myocardial infarction, AV block (first degree), congestive heart failure, arteritis, bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis. **Digestive System:** *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. **Endocrine System:** *Infrequent:* diabetes mellitus, goiter. **Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. **Metabolic and Nutritional Disorders:** *Frequent:* dehydration; *Infrequent:* gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. **Musculoskeletal System:** *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation. **Nervous System:** *Frequent:* delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. **Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. **Skin and Appendages:** *Frequent:* pruritus, diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. **Urogenital System:** *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. **Postintroduction Reports** Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash. **OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.** As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature. **DOSAGE AND ADMINISTRATION** The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day. The higher dose of 10 mg did not provide a statistically significantly greater clinical benefit than 5 mg. There is a suggestion, however, based upon order of group mean scores and dose trend analyses of data from these clinical trials, that a daily dose of 10 mg of ARICEPT® might provide additional benefit for some patients. Accordingly, whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference. Evidence from the controlled trials indicates that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. In open label trials using a 6 week titration, the frequency of these same adverse events was similar between the 5 mg and 10 mg dose groups. Therefore, because steady state is not achieved for 15 days and because the incidence of untoward effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks. ARICEPT® should be taken in the evening, just prior to retiring, and may be taken with or without food.

Revised December 2000

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New York, NY 10017

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Editorial

Bedside test provides food for thought

Is your patient able to eat? Performance testing reveals risk of malnutrition

Fredrick T. Sherman, MD, MSc

How many times have you come to the bedside and found your hospitalized older patient sitting or lying behind a cold, untouched food tray? Why is he or she not eating? The differential diagnosis of this common scenario is broad:

- Is he cognitively impaired from a delirium or dementia?
- Is she sensory-deprived, having misplaced or lost her eyeglasses, hearing aid(s), or dentures?
- Is he diffusely weak from dehydration or a metabolic/electrolyte disorder?
- Does she have upper extremity weakness or tremor or a swallowing dysfunction from an acute or chronic neuromuscular disorder such as a stroke or Parkinson's disease?
- Is he depressed, is his taste impaired from a medication side effect, or does he not like the hospital food ?
- Is nursing staff too busy to assist?

Whatever its etiology, malnutrition has been called acute care's skeleton in the closet. One-fifth of hospitalized older adults who lose any activities of daily living (ADLs) during their acute illness lose the ability to feed themselves.[1] Older adults who cannot feed themselves are at high risk for protein-calorie malnutrition, prolonged hospitalization, nursing home placement, and death. Because feeding is generally the last ADL lost in the cascade that leads to dependency, you usually can be sure that the older adult who cannot feed herself is also unable to bathe, dress, toilet, or transfer.

The bedside assessment

In your bedside assessment of cognition, affect, and physical performance, you should determine whether the older patient can feed herself, swallow properly, and enjoy the taste of food. The untouched food tray or nutritional supplement may well be a tell-tale sign of risk for malnutrition, and it also offers you a useful assessment tool.

If she is awake and alert, I observe my patient drink 1 oz of water from a cup. If she drinks it without interruption or evidence of aspiration (eg, cough or hoarseness), I try a spoonful of applesauce or other pureed food.[2] I watch her dip the spoon in the food, bring it to her mouth, and swallow. Observing her eat helps me assess her ability to recover from the acute illness that led to this hospitalization and the possible need for feeding assistance from other caregivers, including family members, during hospitalization and after discharge.

I help with the feeding only if the patient shows signs of weakness, tremor, or the risk of spilling food and causing embarrassment. Aggressively assisting an older adult who can feed herself encourages learned helplessness and further dependency. "Use it, or lose it" applies to self-feeding as much as to other forms of physical activity.

continued

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Recommendations

Once you are convinced that a patient can feed herself, encourage her to do so. Check her preferences for various flavors and textures of foods and nutritional supplements, and communicate that information to whoever is preparing her food. Meals should be eaten with as few distractions as possible, and conversation while eating should be discouraged to prevent aspiration. Food should be supplied in easy-to-open containers.

I refer patients who fail my bedside feeding tests to the speech or swallowing therapist for further assessment, including videofluoroscopic studies when indicated. If the patient will need ongoing assistance with feeding, I instruct the nurse to teach the family the proper techniques, including sitting posture, head position, size of spoon, speed of feeding, and swallowing precautions.

I never leave a patient's hospital room without assessing his or her ability to eat, either by questioning or performance testing. As a compassionate and caring physician, you owe this to your older patients.

Fredrick T Sherman MD

1. Sager MA, Franke T, Inouye SK, et al. Functional outcomes of acute medical illness and hospitalization in older persons. Arch Intern Med 1996; 156:645-52.
2. Teramoto S, Fukuchi Y. Detection of aspiration and swallowing disorder in older stroke patients: Simple swallowing provocation test versus water swallowing test. Arch Phys Med Rehabil 2000; 81(11):1517-9.

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New in Geriatrics for 2002

New series editor

Geriatrics is pleased to welcome geriatric psychiatrist Gene D. Cohen, MD, PhD, as series editor of "The Psychiatric Consultant." Dr. Cohen is director of the Center on Aging, Health, & Humanities at George Washington University, Washington, DC, where he is professor of health care sciences and professor of psychiatry and behavioral sciences (page 47).

Dr. Cohen

Dr. Weinberger

New CME topic

"The Brain," a series of CME articles on neurologic and psychiatric diseases of aging, begins in this issue with a discussion by Jesse Weinberger, MD, of stroke and transient ischemic attack (page 38). Dr. Weinberger, professor of neurology, and Deborah B. Marin, MD, professor of psychiatry, Mount Sinai School of Medicine, New York, are this year's CME series editors.

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New readers

With this issue, some readers are receiving Geriatrics for the first time. We now reach the more than 7,000 internal medicine and family practice physicians and geriatric psychiatrists who have earned the Certificate of Added Qualifications in Geriatrics from the American Board of Medical Specialties. We welcome these thought-leaders in geriatric medicine, including clinicians, educators, and researchers.

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The most common treatment-emergent adverse events associated with ZYPREXA in schizophrenia trials were somnolence, dizziness, weight gain, personality disorder (COSTART term for nonaggressive objectionable behavior), constipation, akathisia, and postural hypotension. A small number of patients experienced asymptomatic elevations of hepatic transaminase; none of these patients developed jaundice or drug-induced hepatitis. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension.

In a clinical study involving nursing home patients having various psychiatric symptoms in association with Alzheimer's disease, somnolence, abnormal gait, fever, dehydration, and back pain were observed more often with ZYPREXA than with placebo. As with other CNS-active drugs, ZYPREXA should be used with caution in elderly patients with dementia.

Phenylketonurics: ZYPREXA Zydis contains phenylalanine.

*Indicated for the treatment of schizophrenia.

See adjacent Brief Summary of Prescribing Information for indications, warnings/precautions, and dosing information.

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Brief Summary: Please consult package insert for complete prescribing information.

INDICATIONS AND USAGE: For the treatment of schizophrenia. Efficacy of oral ZYPREXA at maintaining treatment response for up to 8 months in schizophrenic patients has been demonstrated. For the short-term treatment of acute manic episodes associated with Bipolar I Disorder.

CONTRAINDICATIONS: Known hypersensitivity to olanzapine.

WARNINGS: Neuroleptic Malignant Syndrome (NMS)—NMS is a potentially fatal symptom complex that has been reported in association with administration of antipsychotic drugs, including olanzapine. Management includes immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; intensive symptomatic treatment and medical monitoring; and treatment of any concomitant serious medical problems as appropriate. Patients requiring antipsychotic drug treatment after recovery from NMS should be carefully monitored since recurrences have been reported.

Tardive Dyskinesia (TD)—A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to predict, at the inception of antipsychotic treatment, which patients are more likely to develop the syndrome. If signs and symptoms of TD appear in a patient on olanzapine, consider drug discontinuation.

PRECAUTIONS: Orthostatic Hypotension—Olanzapine may induce orthostatic hypotension associated with dizziness; tachycardia; and in some patients, syncope (incidence, 0.6%, 15/2500). These risks may be minimized by initiating therapy with 5 mg QD and titrating more gradually to target dose when hypotension occurs. Use with particular caution in patients with known cardiovascular disease, cerebrovascular disease, and conditions which predispose to hypotension.

Seizures—During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients, regardless of causality. Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

Hyperprolactinemia—As with other drugs that antagonize dopamine D_2 receptors, olanzapine elevates prolactin levels; a modest elevation persists during chronic administration.

Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro. However, neither clinical nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive.

Transaminase Elevations—In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of normal) were observed in 2% (6/243) of patients exposed to olanzapine compared to none (0/115) of the placebo patients. None of these patients experienced jaundice. In two of these patients, liver enzymes decreased toward normal despite continued treatment and in two others, enzymes decreased upon discontinuation of olanzapine. The fifth patient, seropositive for hepatitis C, had persistent enzyme elevation for 4 months after discontinuation; the sixth had insufficient follow-up to determine if enzymes normalized.

Among about 2400 patients with baseline SGPT ≤90 IU/L, 2% (50/2381) had asymptomatic SGPT elevations to >200 IU/L. Most were transient changes that tended to normalize while olanzapine treatment was continued. Among all 2500 clinical trial patients, about 1% (23/2500) discontinued treatment due to transaminase increases.

Exercise caution in patients who have signs and symptoms of hepatic impairment, preexisting conditions associated with limited hepatic functional reserve; or concomitant treatment with potentially hepatotoxic drugs (*see* Laboratory Tests, below).

Potential for Cognitive and Motor Impairment—Somnolence was a commonly reported (olanzapine 26% vs placebo 15%), dose-related adverse event associated with olanzapine in premarketing trials. Somnolence led to discontinuation in 0.4% (9/2500) of patients (*see* Information for Patients, below).

Body Temperature Regulation—Use appropriate care when prescribing olanzapine for patients who will be experiencing conditions that may contribute to an elevation in core body temperature.

Dysphagia—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Two olanzapine-treated patients (2/407) in 2 studies in patients with Alzheimer's disease died from aspiration pneumonia during or within 30 days of the termination of the double-blind portion of their respective studies; there were no deaths in placebo-treated patients. One of these patients had experienced dysphagia prior to the development of aspiration pneumonia. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide—The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Concomitant Illnesses—Olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In a fixed-dose study of olanzapine 5, 10, and 15 mg/day and placebo in nursing home patients (mean age 83 years) having various psychiatric symptoms in association with Alzheimer's disease, the following treatment-emergent adverse events were reported in each and every olanzapine-treated group at an incidence of twofold or more in excess of the placebo-treated group or in at least 2 olanzapine patients if no placebo-treated patient was reported to have experienced the event: somnolence, abnormal gait, fever, dehydration, back pain. Discontinuations (olanzapine vs placebo) due to abnormal gait (1% vs 0%), accidental injury (1% vs 0%), and somnolence (3% vs 0%) were considered drug related. As with other CNS-active drugs, use olanzapine with caution in elderly patients with dementia.

Because of the risk of orthostatic hypotension with olanzapine, use caution in cardiac patients.

Information for Patients—Patients should be advised of the risk of orthostatic hypotension, especially during the initial titration period and with concomitant drugs that may potentiate the orthostatic effect of olanzapine (e.g., diazepam, alcohol). Caution patients about operating hazardous machinery, including automobiles, until they determine that therapy with olanzapine does not affect them adversely. Advise patients to notify their physician if they become or intend to become pregnant during therapy with olanzapine; not to breast-feed an infant; to avoid alcohol; and to inform their physicians of any prescription or OTC medications they are taking or plan to take. Advise patients regarding appropriate care in avoiding overheating and dehydration. Advise phenylketonurics that ZYPREXA ZYDIS tablets contain phenylalanine.

Laboratory Tests—Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

Drug Interactions—Use caution when olanzapine is taken in combination with other centrally acting drugs and alcohol. Olanzapine may enhance the effects of certain antihypertensive agents. Olanzapine may antagonize the effects of levodopa and dopamine agonists. Agents that induce CYP1A2 or glucuronyl transferase enzymes (e.g., omeprazole, rifampin) may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 (e.g., fluvoxamine) could potentially inhibit olanzapine elimination. Because olanzapine is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease olanzapine clearance. Activated charcoal (1 g) reduced the C_{max} and AUC of olanzapine by about 60%. Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine. Carbamazepine (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance. Neither ethanol (45 mg/70 kg single dose) nor warfarin (20 mg single dose) had an effect on olanzapine pharmacokinetics. Fluoxetine at 60 mg (single or multiple doses) causes a small increase in the C_{max} of olanzapine and a small decrease in olanzapine clearance; however, the impact of this factor is small in comparison to the overall variability between individuals, and dose modification is not routinely recommended. In vitro data suggest a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Olanzapine is unlikely to cause clinically important drug interactions mediated by the enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Single doses of olanzapine did not affect the pharmacokinetics of imipramine/desipramine or warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam/N-desmethyldiazepam, lithium, ethanol, or biperiden. However, coadministration of either diazepam or ethanol potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites.

Carcinogenesis, Mutagenesis, Impairment of Fertility—The incidence of liver hemangiomas and hemangiosarcomas in female mice was significantly increased in one carcinogenicity study at 2 times the maximum human dose (mg/m² basis), but not in another study at 2-5 times the maximum human dose (mg/m² basis). In this study there was a high incidence of early mortalities in males in the 30/20 mg/kg/day group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice given olanzapine at 0.5 times the maximum human dose (mg/m² basis), and in female rats at 2 times the maximum human dose (mg/m² basis). In other studies, serum prolactin measurements of olanzapine showed elevations up to 4-fold in rats at the same doses used in the carcinogenicity studies. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown. No evidence of mutagenic potential for olanzapine has been found.

In rats, male mating performance was impaired at a dose of 11 times the maximum recommended human daily dose (mg/m² basis) and female fertility was decreased at a dose of 1.5 times the maximum human daily dose (mg/m² basis). Discontinuance of treatment reversed the effects on male mating performance. In female rats the precoital period was increased and the mating index reduced at 2.5 times the maximum human dose (mg/m² basis). Diestrous was prolonged and estrous delayed at 0.6 times the maximum human dose (mg/m² basis); therefore, olanzapine may produce a delay in ovulation.

Pregnancy Category C—In rats and rabbits at doses equivalent to 9 and 30 times the maximum recommended human daily dose respectively (on an mg/m² basis), no evidence of teratogenicity was observed. In rats, early resorptions and increased numbers of nonviable fetuses were observed at 9 times the maximum human dose (mg/m² basis), and gestation was prolonged at 5 times the maximum human dose (mg/m² basis). In rabbits, fetal toxicity (increased resorptions and decreased fetal weight) occurred at a maternally toxic dose of 30 times the maximum human dose (mg/m² basis). Placental transfer occurs in rat pups.

There are no adequate and well-controlled studies in pregnant women. Olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Parturition in rats was not affected by olanzapine; its effect on labor and delivery in humans is unknown.

Olanzapine was excreted in milk of lactating rats. It is not known if olanzapine is excreted in human milk; women receiving olanzapine should not breast-feed.

Use in Pediatric and Geriatric Patients—Safety and effectiveness in pediatric patients have not been established.

In patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in patients with various psychiatric symptoms in association with Alzheimer's disease have suggested there may be a different tolerability profile in these patients. As with other CNS-active drugs, use with caution in elderly patients with dementia. Consider a lower starting dose for any geriatric patient in the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine (*see* PRECAUTIONS and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: The following findings are based on a clinical trial database consisting of 4189 patients with approximately 2665 patient-years of exposure, including patients with schizophrenia, bipolar mania, or Alzheimer's disease. See the full prescribing information for details on these trials.

Associated with Discontinuation—Overall there was no difference in the incidence of discontinuation due to adverse events (olanzapine vs placebo: schizophrenia, 5% vs 6%, bipolar mania 2% vs 2%). Discontinuations in schizophrenia trials due to increases in SGPT were considered to be drug related (olanzapine 2% vs placebo 0%; *see* PRECAUTIONS).

Commonly Observed Adverse Events—In 6-week, placebo-controlled, premarketing schizophrenia trials, the most common treatment-emergent adverse events associated with olanzapine (incidence ≥5% and not observed at an equivalent incidence with placebo; olanzapine incidence at least twice that for placebo) were: postural hypotension, constipation, weight gain, dizziness, personality disorder (COSTART term for nonaggressive objectionable behavior), and akathisia. In 3- and 4-week placebo-controlled bipolar mania trials, the most common treatment-emergent adverse events associated with olanzapine were: asthenia, dry mouth, constipation, dyspepsia, increased appetite, somnolence, dizziness, and tremor.

Adverse Events with an Incidence ≥2%—The following treatment-emergent events were reported at an incidence of ≤2% with olanzapine (≥2.5 mg/day), and at a greater incidence with olanzapine than with placebo in short-term placebo-controlled trials in patients with schizophrenia, bipolar mania, or Alzheimer's disease (olanzapine N=532, placebo N=294): *Body as a Whole*—accidental injury, asthenia, fever, back pain, chest pain; *Cardiovascular*—postural hypotension, tachycardia, hypertension; *Digestive*—dry mouth, constipation, dyspepsia, vomiting, increased appetite; *Hemic and Lymphatic*—ecchymosis; *Metabolic and Nutritional*—weight gain, peripheral edema; *Musculoskeletal*—extremity pain (other than joint), joint pain; *Nervous System*—somnolence, insomnia, dizziness, abnormal gait, tremor, akathisia, hypertonia, articulation impairment; *Respiratory*—rhinitis, cough increased, pharyngitis; *Special Senses*—amblyopia; *Urogenital*—urinary incontinence, urinary tract infection.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms: In an acute-phase controlled clinical trial comparing placebo and 3 fixed daily doses of olanzapine (5±2.5, 10±2.5, 15±2.5 mg) in schizophrenia, the incidence of treatment-emergent EPS was assessed by categorical analyses of formal rating scales. There was no significant difference between any dose of olanzapine and placebo in the incidence of parkinsonism (patients with a Simpson-Angus Scale total score >3) or akathisia (patients with a Barnes Akathisia global score ≥2).

In the same clinical trial, when treatment-emergent EPS was assessed by spontaneously reported adverse event terms, only akathisia events (COSTART terms akathisia and hyperkinesia) showed a statistically significantly greater incidence with the 2 higher doses of olanzapine than with placebo. The incidence of patients reporting any extrapyramidal event was significantly greater than placebo only with the highest dose of olanzapine (15±2.5 mg/day).

Other Adverse Events: Dose-relatedness of adverse events was assessed using data from a clinical trial involving 3 fixed dosage ranges. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

Vital Sign Changes—Olanzapine is associated with orthostatic hypotension and tachycardia (*see* PRECAUTIONS).

Weight Gain—In placebo-controlled 6-week schizophrenia studies, weight gain was reported in 5.6% of olanzapine patients (average 2.8-kg gain) compared to 0.8% of placebo patients (average 0.4-kg loss); 29% of olanzapine patients gained greater than 7% of their baseline weight, compared to 3% of placebo patients.

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine treatment in the premarketing database.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following COSTART terms reflect treatment-emergent events reported with olanzapine at multiple doses ≥1 mg/day in clinical trials (4189 patients; 2665 patient-years of exposure). Although these events occurred during treatment with olanzapine, they were not necessarily caused by it. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients.

Body as a Whole—*Frequent*: dental pain, flu syndrome, intentional injury, suicide attempt; *Infrequent*: abdomen enlarged, chills, chills and fever, face edema, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction; *Rare*: hangover effect, sudden death.

Cardiovascular—*Infrequent*: hypotension; *Infrequent*: bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare*: arteritis, atrial fibrillation, heart failure, pulmonary embolus.

Digestive—*Frequent*: increased salivation, thirst; *Infrequent*: dysphagia, eructation, fecal impaction, fecal incontinence, flatulence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare*: aphthous stomatitis, enteritis, esophageal ulcer, esophagitis, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration.

Endocrine—*Infrequent*: diabetes mellitus; *Rare*: diabetic acidosis, goiter.

Hemic and Lymphatic—*Frequent*: leukopenia; *Infrequent*: anemia, cyanosis, leukocytosis, lymphadenopathy, thrombocythemia, thrombocytopenia; *Rare*: normocytic anemia.

Metabolic and Nutritional—*Infrequent*: acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema, water intoxication; *Rare*: gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis.

Musculoskeletal—*Frequent*: joint stiffness, twitching; *Infrequent*: arthritis, arthrosis, bursitis, leg cramps, myasthenia; *Rare*: bone pain, myopathy, osteoporosis, rheumatoid arthritis.

Nervous System—*Frequent*: abnormal dreams, emotional lability, euphoria, libido decreased, paresthesia, schizophrenic reaction; *Infrequent*: alcohol misuse, amnesia, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, coma, delirium, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, tobacco misuse, vertigo, withdrawal syndrome; *Rare*: akinesia, circumoral paresthesia, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage.

Respiratory—*Frequent*: dyspnea; *Infrequent*: apnea, aspiration pneumonia, asthma, atelectasis, epistaxis, hemoptysis, hyperventilation, laryngitis, pneumonia, voice alteration; *Rare*: hiccup, hypoventilation, hypoxia, lung edema, stridor.

Skin and Appendages—*Frequent*: sweating; *Infrequent*: alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin ulcer, vesiculobullous rash; *Rare*: hirsutism, pustular rash, skin discoloration, urticaria.

Special Senses—*Frequent*: conjunctivitis; *Infrequent*: abnormality of accommodation, blepharitis, cataract, corneal lesion, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare*: glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens.

Urogenital—*Frequent*: amenorrhea,* hematuria, metrorrhagia,* vaginitis*; *Infrequent*: abnormal ejaculation,* breast pain, cystitis, decreased menstruation,* dysuria, female lactation, glycosuria, impotence,* increased menstruation,* menorrhagia,* polyuria, premenstrual syndrome,* pyuria, urinary frequency, urinary retention, urination impaired, uterine fibroids enlarged,* vaginal hemorrhage*; *Rare*: albuminuria, gynecomastia, mastitis, oliguria, urinary urgency.

(* Adjusted for gender.)

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to ZYPREXA therapy: diabetic coma and priapism.

DRUG ABUSE AND DEPENDENCE: Olanzapine is not a controlled substance. In animal studies, olanzapine was shown to have little or no potential of abuse or physical dependence at oral doses 8 to 15 times the maximum daily human dose (on an mg/m² basis). While clinical trials in humans did not reveal any tendency for any drug-seeking behavior, it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Evaluate patients carefully for a history of drug abuse, and observe such patients closely for signs of misuse or abuse of olanzapine.

DOSAGE AND ADMINISTRATION: Usual Dose—Administer once daily without regard to meals. Schizophrenia: Begin with 5-10 mg/day with a target dose of 10 mg/day within several days. Dosage adjustments, if indicated, should occur at intervals of not less than 1 week. Bipolar mania: Begin with 10 or 15 mg/day. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours.

Special Populations—Schizophrenia and bipolar mania: The recommended starting dose is 5 mg in patients who are debilitated, who have a predisposition to hypotensive reactions, who otherwise exhibit a combination of factors that may result in slower metabolism of olanzapine, or who may be more pharmacodynamically sensitive to olanzapine.

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Geriatrics®

Medicine for Midlife and Beyond

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Cover illustration by David Baker

Infectious disease

28 Influenza

How to prevent and control nursing home outbreaks

Irving H. Gomolin, MD Rakesh K. Kathpalia, MD

Influenza is an important cause of acute respiratory illness among older adults, particularly within the nursing home. These authors describe the clinical features of influenza and its atypical presentations in older patients, the use of rapid diagnostic techniques, the utility of late-season vaccinations, and a treatment and prophylaxis strategy to control suspected influenza outbreaks in the nursing home.

Series introduction

37 Brain function in aging: Solutions for significant challenges

Jesse Weinberger, MD Deborah B. Marin, MD

Neurologic and psychiatric disorders contribute to mental and physical decline in older patients and pose a clinical challenge for physicians. In this issue, a new CME series called "The Brain" begins with a discussion of prevention and management of stroke and TIA (see below). Series editors are Jesse Weinberger, MD, professor, department of neurology, and Deborah B. Marin, MD, professor and vice chair, department of psychiatry at Mount Sinai School of Medicine, New York, the ACCME-accredited sponsor of this CME activity.

CME Geriatrics The Brain

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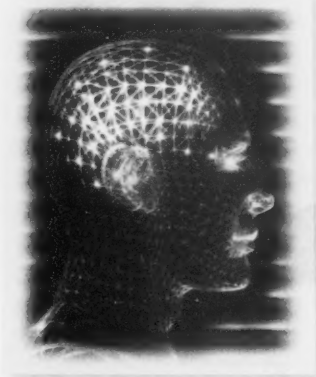

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The Brain

38 Stroke and TIA

Prevention and management of cerebrovascular events in primary care

Jesse Weinberger, MD

Stroke is the third-leading cause of death in the United States and the leading cause of neurologic disability. Persons with a history of transient ischemic attacks (TIAs) are at increased risk for stroke. In this CME article, Dr. Weinberger describes the primary care physician's key role in stroke prevention, which begins with helping older patients modify controllable risk factors such as hypertension, diabetes, and hyperlipidemia. He also details effective pharmacologic and surgical approaches for reducing the risk of stroke and managing emergent cerebrovascular events.

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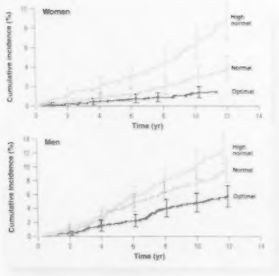

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Please see brief summary of prescribing information on next page.

Brief Summary
NORVASC® (amlodipine besylate) Tablets

For Oral Use

CONTRAINDICATIONS: NORVASC is contraindicated in patients with known sensitivity to amlodipine.

WARNINGS: Increased Angina and/or Myocardial Infarction: Rarely, patients, particularly those with severe obstructive coronary artery disease, have developed documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting calcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not been elucidated.

PRECAUTIONS: General: Since the vasodilation induced by NORVASC is gradual in onset, acute hypotension has rarely been reported after oral administration of NORVASC. Nonetheless, caution should be exercised when administering NORVASC as with any other peripheral vasodilator particularly in patients with severe aortic stenosis.

Use in Patients with Congestive Heart Failure: In general, calcium channel blockers should be used with caution in patients with heart failure. NORVASC (5-10 mg per day) has been studied in a placebo-controlled trial of 1153 patients with NYHA Class III or IV heart failure on stable doses of ACE inhibitor, digoxin, and diuretics. Follow-up was at least 6 months, with a mean of about 14 months. There was no overall adverse effect on survival or cardiac morbidity (as defined by life-threatening arrhythmia, acute myocardial infarction, or hospitalization for worsened heart failure). NORVASC has been compared to placebo in four 8-12 week studies of patients with NYHA Class II/III heart failure, involving a total of 697 patients. In these studies, there was no evidence of worsened heart failure based on measures of exercise tolerance, NYHA classification, symptoms, or LVEF.

Beta-Blocker Withdrawal: NORVASC is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

Patients with Hepatic Failure: Since NORVASC is extensively metabolized by the liver and the plasma elimination half-life ($t_{1/2}$) is 56 hours in patients with impaired hepatic function, caution should be exercised when administering NORVASC to patients with severe hepatic impairment.

Drug Interactions: *In vitro* data in human plasma indicate that NORVASC has no effect on the protein binding of drugs tested (digoxin, phenytoin, warfarin, and indomethacin).

Special Studies: Effect of other agents on NORVASC: CIMETIDINE: co-administration of NORVASC with cimetidine did not alter the pharmacokinetics of NORVASC. GRAPEFRUIT JUICE: co-administration of 240 mL of grapefruit juice with a single oral dose of amlodipine 10 mg in 20 healthy volunteers had no significant effect on the pharmacokinetics of amlodipine. MAALOX (antacid): co-administration of the antacid Maalox with a single dose of NORVASC had no significant effect on the pharmacokinetics of NORVASC. SILDENAFIL: a single 100 mg dose of sildenafil (Viagra®) in subjects with essential hypertension had no effect on the pharmacokinetic parameters of NORVASC. When NORVASC and sildenafil were used in combination, each agent independently exerted its own blood pressure lowering effect.

Special Studies: Effect of NORVASC on other agents: ATORVASTATIN: co-administration of multiple 10 mg doses of NORVASC with 80 mg of atorvastatin resulted in no significant change in the steady state pharmacokinetic parameters of atorvastatin. DIGOXIN: co-administration of NORVASC with digoxin did not change serum digoxin levels or digoxin renal clearance in normal volunteers. ETHANOL (alcohol): single and multiple 10 mg doses of NORVASC had no significant effect on the pharmacokinetics of ethanol. WARFARIN: co-administration of NORVASC with warfarin did not change the warfarin prothrombin response time.

In clinical trials, NORVASC has been safely administered with thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, long-acting nitrates, sublingual nitroglycerin, digoxin, warfarin, non-steroidal anti-inflammatory drugs, antibiotics, and oral hypoglycemic drugs.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Rats and mice treated with amlodipine in the diet for two years, at concentrations calculated to provide daily dosage levels of 0.5, 1.25, and 2.5 mg/kg/day showed no evidence of carcinogenicity. The highest dose (for mice, similar to, and for rats twice* the maximum recommended clinical dose of 10 mg on a mg/m² basis) was close to the maximum tolerated dose for mice but not for rats.

Mutagenicity studies revealed no drug related effects at either the gene or chromosome levels.

There was no effect on the fertility of rats treated with amlodipine (males for 64 days and females 14 days prior to mating) at doses up to 10 mg/kg/day (8 times* the maximum recommended human dose of 10 mg on a mg/m² basis).

Pregnancy Category C: No evidence of teratogenicity or other embryo/fetal toxicity was found when pregnant rats or rabbits were treated orally with up to 10 mg/kg amlodipine (respectively 8 times* and 23 times* the maximum recommended human dose of 10 mg on a mg/m² basis) during their respective periods of major organogenesis. However, litter size was significantly decreased (by about 50%) and the number of intrauterine deaths was significantly increased (about 5-fold) in rats administered 10 mg/kg amlodipine for 14 days before mating and throughout mating and gestation. Amlodipine has been shown to prolong both the gestation period and the duration of labor in rats at this dose. There are no adequate and well-controlled studies in pregnant women. Amlodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether amlodipine is excreted in human milk. In the absence of this information, it is recommended that nursing be discontinued while NORVASC is administered.

Pediatric Use: Safety and effectiveness of NORVASC in children have not been established.

Geriatric Use: Clinical studies of NORVASC did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Elderly patients have decreased clearance of amlodipine with a resulting increase of AUC of approximately 40-60%, and a lower initial dose may be required (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS: NORVASC has been evaluated for safety in more than 11,000 patients in U.S. and foreign clinical trials. In general, treatment with NORVASC was well-tolerated at doses up to 10 mg daily. Most adverse reactions reported during therapy with NORVASC were of mild or moderate severity. In controlled clinical trials directly comparing NORVASC (N=1730) in doses up to 10 mg to placebo (N=1250), discontinuation of NORVASC due to adverse reactions was required in only about 1.5% of patients and was not significantly different from placebo (about 1%). The most common side effects are headache and edema. The incidence (%) of side effects which occurred in a dose related manner are as follows: edema (1.8% at 2.5 mg, 3.0% at 5.0 mg, and 10.8% at 10.0 mg, compared with 0.6% placebo); dizziness (1.1% at 2.5 mg, 3.4% at 5.0 mg, and 3.4% at 10.0 mg, compared with 1.5% placebo); flushing (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 2.6% at 10.0 mg, compared with 0.0% placebo); and palpitation (0.7% at 2.5 mg, 1.4% at 5.0 mg, and 4.5% at 10.0 mg, compared with 0.6% placebo).

Other adverse experiences which were not clearly dose related but which were reported with an incidence greater than 1.0% in placebo-controlled clinical trials include the following: headache (7.3%, compared with 7.8% placebo); fatigue (4.5%, compared with 2.8% placebo); nausea (2.9%, compared with 1.9% placebo); abdominal pain (1.6%, compared with 0.3% placebo); and somnolence (1.4%, compared with 0.6% placebo).

For several adverse experiences that appear to be drug and dose related, there was a greater incidence in women than men associated with amlodipine treatment as follows: edema (5.6% in men, 14.6% in women, compared with a placebo incidence in men of 1.4% and 5.1% in women); flushing (1.5% in men, 4.5% in women, compared with a placebo incidence of 0.3% in men and 0.9% in women); palpitations (1.4% in men, 3.3% in women, compared with a placebo incidence of 0.9% in men and 0.9% in women); and somnolence (1.3% in men, 1.6% in women, compared with a placebo incidence of 0.8% in men and 0.3% in women).

The following events occurred in ≤1% but >0.1% of patients in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis; **central and peripheral nervous system:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo; **gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia; **general:** allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain; **musculoskeletal system:** arthralgia, arthrosis, muscle cramps,** myalgia; **psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization; **respiratory system:** dyspnea,** epistaxis; **skin and appendages:** angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular; **special senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus; **urinary system:** micturition frequency, micturition disorder, nocturia; **autonomic nervous system:** dry mouth, sweating increased; **metabolic and nutritional:** hyperglycemia, thirst; **hemopoietic:** leukopenia, purpura, thrombocytopenia.

The following events occurred in ≤0.1% of patients: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia.

Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina.

NORVASC therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine.

The following postmarketing event has been reported infrequently where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine.

NORVASC has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles.

OVERDOSAGE: Single oral doses of 40 mg/kg and 100 mg/kg in mice and rats, respectively, caused deaths. A single oral dose of 4 mg/kg or higher in dogs caused a marked peripheral vasodilation and hypotension.

Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of NORVASC is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted.

If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit.

* Based on patient weight of 50 kg.

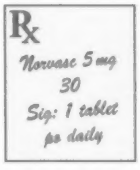
**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

More detailed professional information available on request.
Revised April 2000

Once-Daily 5-mg and 10-mg tablets

NORVASC®

(amlodipine besylate)



The most prescribed cardiovascular agent in the world[4*]

***Among branded cardiovascular agents indicated for hypertension and/or angina.[4]**

References: 1. Velasco M, Urbina A, Silva H, et al. A double-blind, parallel, comparative evaluation of amlodipine vs. captopril in the monotherapeutic treatment of mild and moderate essential hypertension. *J Cardiovasc Pharmacol.* 1991;17(suppl 1):S19-S21. **2.** Kloner RA, Sowers JR, DiBona GF, Gaffney M, Wein M, for the Amlodipine Cardiovascular Community Trial Study Group. Sex- and age-related antihypertensive effects of amlodipine. *Am J Cardiol.* 1996;77:713-722. **3.** Hayduk K, Adamczak M, Nowitzki G. Is initial dose titration of amlodipine worthwhile in patients with mild to moderate hypertension? *Curr Med Res Opin.* 1999;15:39-45. **4.** IMS International Prescription Data (based on 29 countries), December 1999; IMS National Prescription Audit (total prescriptions), YTD May 2000; IMS Midas Data, 4Q99.

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For an Alzheimer's disease patient...

Just achieving the ordinary can be extraordinary

Reference: 1. EXELON® [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2000.

Please see brief summary of complete prescribing information on the adjacent page.

NOVARTIS

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EXELON...The first choice that stays the course

- Proven efficacy in global functioning, based on evaluation of 3 key domains of Alzheimer's disease...*[1]

  Activities of daily living Behavior Cognition

- Dosing flexibility allows customized treatment[1]
  - *Simple 1-step dosing to therapeutic dosage range*
  - *Clear dose response that can maximize efficacy*[1]
    - *Higher doses can be associated with increased incidence of adverse events, especially during dose titration*

- Established safety profile
  - *Minimal metabolism by the CYP450 isoenzyme system*[1]
  - *No clinically significant drug interactions in clinical trials*[1]
  - *No dosage adjustment needed for patients with renal or hepatic impairment*[1]

For mild to moderate Alzheimer's disease

EXELON®
(rivastigmine tartrate)

1.5, 3, 4.5, 6 mg Capsules
2 mg/mL Oral Solution

More than memories

*Measured by the Clinician's Interview-Based Impression of Change With Caregiver Input (CIBIC-Plus).

In controlled clinical trials, the most common adverse events were nausea, vomiting, anorexia, dyspepsia, and asthenia. **EXELON use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. If therapy is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose in order to avoid the possibility of severe vomiting and its potentially serious sequelae.** In the controlled trials, 47% of patients experienced nausea and 31% of patients experienced vomiting. Weight loss associated with EXELON occurred more commonly among women receiving high doses in clinical trials. Due to increased cholinergic activity, cholinesterase inhibitors may be expected to increase gastric acid secretion and/or have vagotonic effects on heart rate. Therefore, EXELON should be used with caution in patients with peptic ulcers, gastrointestinal bleeding, and "sick sinus syndrome" or other supraventricular cardiac conduction conditions. (Please see important WARNINGS in brief summary of full prescribing information.)

Exelon®

(rivastigmine tartrate)

Capsules

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

INDICATIONS AND USAGE: Exelon® (rivastigmine tartrate) is indicated for the treatment of mild to moderate dementia of the Alzheimer's type.

CONTRAINDICATIONS: Exelon® (rivastigmine tartrate) is contraindicated in patients with known hypersensitivity to rivastigmine, other carbamate derivatives or other components of the formulation *(see DESCRIPTION in the full prescribing information)*.

WARNINGS: Gastrointestinal Adverse Reactions: Exelon® (rivastigmine tartrate) use is associated with significant gastrointestinal adverse reactions, including nausea and vomiting, anorexia, and weight loss. For this reason, patients should always be started at a dose of 1.5 mg BID and titrated to their maintenance dose. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose *(see DOSAGE AND ADMINISTRATION in the full prescribing information)* to reduce the possibility of severe vomiting and its potentially serious sequelae (e.g., there has been one post-marketing report of severe vomiting with esophageal rupture following inappropriate reinitiation of treatment with a 4.5-mg dose after 8 weeks of treatment interruption).

***Nausea and Vomiting:* In the controlled clinical trials, 47% of the patients treated with an Exelon dose in the therapeutic range of 6-12 mg/day (n=1189) developed nausea (compared with 12% in placebo). A total of 31% of Exelon-treated patients developed at least one episode of vomiting (compared with 5% for placebo). The rate of vomiting was higher during the titration phase (24% vs. 3% for placebo) than in the maintenance phase (14% vs. 3% for placebo). The rates were higher in women than men. Five percent of patients discontinued for vomiting, compared to less than 1% for patients on placebo. Vomiting was severe in 2% of Exelon-treated patients and was rated as mild or moderate each in 14% of patients. The rate of nausea was higher during the titration phase (43% vs. 9% for placebo) than in the maintenance phase (17% vs. 4% for placebo).**

***Weight Loss:* In the controlled trials, approximately 26% of women on high doses of Exelon (greater than 9 mg/day) had weight loss of equal to or greater than 7% of their baseline weight compared to 6% in the placebo-treated patients. About 18% of the males in the high dose group experienced a similar degree of weight loss compared to 4% in placebo-treated patients. It is not clear how much of the weight loss was associated with anorexia, nausea, vomiting, and the diarrhea associated with the drug.**

Anorexia: In the controlled clinical trials, of the patients treated with an Exelon dose of 6-12 mg/day, 17% developed anorexia compared to 3% of the placebo patients. Neither the time course or the severity of the anorexia is known.

Peptic Ulcers/Gastrointestinal Bleeding: Because of their pharmacological action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of Exelon have shown no significant increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding.

Anesthesia: Exelon as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Cardiovascular Conditions: Drugs that increase cholinergic activity may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. In clinical trials, Exelon was not associated with any increased incidence of cardiovascular adverse events, heart rate or blood pressure changes, or ECG abnormalities. Syncopal episodes have been reported in 3% of patients receiving 6-12 mg/day of Exelon, compared to 2% of placebo patients.

Genitourinary: Although this was not observed in clinical trials of Exelon, drugs that increase cholinergic activity may cause urinary obstruction.

Neurological Conditions: Seizures: Drugs that increase cholinergic activity are believed to have some potential for causing seizures. However, seizure activity also may be a manifestation of Alzheimer's Disease.

Pulmonary Conditions: Like other drugs that increase cholinergic activity, Exelon should be used with care in patients with a history of asthma or obstructive pulmonary disease.

PRECAUTIONS: Information for Patients and Caregivers: Caregivers should be advised of the high incidence of nausea and vomiting associated with the use of the drug along with the possibility of anorexia and weight loss. Caregivers should be encouraged to monitor for these adverse events and inform the physician if they occur. It is critical to inform caregivers that if therapy has been interrupted for more than several days, the next dose should not be administered until they have discussed this with the physician.

Drug-Drug Interactions: ***Effect of Exelon® (rivastigmine tartrate) on the Metabolism of Other Drugs:*** Rivastigmine is primarily metabolized through hydrolysis by esterases. Minimal metabolism occurs via the major cytochrome P450 isoenzymes. Based on *in vitro* studies, no pharmacokinetic drug interactions with drugs metabolized by the following isoenzyme systems are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.

No pharmacokinetic interaction was observed between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine in studies in healthy volunteers. The elevation of prothrombin time induced by warfarin is not affected by administration of Exelon.

Effect of Other Drugs on the Metabolism of Exelon: Drugs that induce or inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine. Single dose pharmacokinetic studies demonstrated that the metabolism of rivastigmine is not significantly affected by concurrent administration of digoxin, warfarin, diazepam, or fluoxetine.

Population PK analysis with a database of 625 patients showed that the pharmacokinetics of rivastigmine were not influenced by commonly prescribed medications such as antacids (n=77), antihypertensives (n=72), β-blockers (n=42), calcium channel blockers (n=75), antidiabetics (n=21), nonsteroidal anti-inflammatory drugs (n=79), estrogens (n=70), salicylate analgesics (n=177), antianginals (n=35), and antihistamines (n=15).

Use with Anticholinergics: Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications.

Use with Cholinomimetics and Other Cholinesterase Inhibitors: A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In carcinogenicity studies conducted at dose levels up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic. These dose levels are approximately 0.9 times and 0.7 times the maximum recommended human daily dose of 12 mg/day on a mg/m^2 basis.

Rivastigmine was clastogenic in two *in vitro* assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three *in vitro* assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the *in vivo* mouse micronucleus test.

Rivastigmine had no effect on fertility or reproductive performance in the rat at dose levels up to 1.1 mg-base/kg/day. This dose is approximately 0.9 times the maximum recommended human daily dose of 12 mg/day on a mg/m^2 basis.

Pregnancy: ***Pregnancy Category B:*** Reproduction studies conducted in pregnant rats at doses up to 2.3 mg-base/kg/day (approximately 2 times the maximum recommended human dose on a mg/m^2 basis) and in pregnant rabbits at doses up to 2.3 mg-base/kg/day (approximately 4 times the maximum recommended human dose on a mg/m^2 basis) revealed no evidence of teratogenicity. Studies in rats showed slightly decreased fetal/pup weights, usually at doses causing some maternal toxicity; decreased weights were seen at doses which were several fold lower than the maximum recommended human dose on a mg/m^2 basis. There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Exelon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether rivastigmine is excreted in human breast milk. Exelon has no indication for use in nursing mothers.

Pediatric Use: There are no adequate and well-controlled trials documenting the safety and efficacy of Exelon in any illness occurring in children.

ADVERSE REACTIONS: Adverse Events Leading to Discontinuation: The rate of discontinuation due to adverse events in controlled clinical trials of Exelon® (rivastigmine tartrate) was 15% for patients receiving 6-12 mg/day compared to 5% for patients on placebo during forced weekly dose titration. While on a maintenance dose, the rates were 6% for patients on Exelon compared to 4% for those on placebo.

The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Clinical Trials during Titration and Maintenance in Patients Receiving 6-12 mg/day Exelon® Using a Forced Dose Titration

Study Phase	Titration		Maintenance		Overall	
	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1189)	Placebo (n=788)	Exelon ≥6-12 mg/day (n=987)	Placebo (n=868)	Exelon ≥6-12 mg/day (n=1189)
Event / % Discontinuing						
Nausea	<1	8	<1	1	1	8
Vomiting	<1	4	<1	1	<1	5
Anorexia	0	2	<1	1	<1	3
Dizziness	<1	2	<1	1	<1	2

Most Frequent Adverse Clinical Events Seen in Association with the Use of Exelon: The most common adverse events, defined as those occurring at a frequency of at least 5% and twice the placebo rate, are largely predicted by Exelon's cholinergic effects. These include nausea, vomiting, anorexia, dyspepsia, and asthenia.

Gastrointestinal Adverse Reactions: Exelon use is associated with significant nausea, vomiting, and weight loss *(see WARNINGS)*.

Adverse Events Reported in Controlled Trials: Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials and for which the rate of occurrence was greater for patients treated with Exelon doses of 6-12 mg/day than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the frequency of adverse events in the course of usual medical practice when patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses, or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis by which to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

In general, adverse reactions were less frequent later in the course of treatment.

No systematic effect of race or age could be determined on the incidence of adverse events in the controlled studies. Nausea, vomiting and weight loss were more frequent in women than men.

Table 2. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Exelon® (6-12 mg/day) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=868)	Exelon (6-12 mg/day) (n=1189)
Percent of Patients with any Adverse Event	79	92
Autonomic Nervous System		
Sweating increased	1	4
Syncope	2	3
Body as a Whole		
Accidental Trauma	9	10
Fatigue	5	9
Asthenia	2	6
Malaise	2	5
Influenza-like Symptoms	2	3
Weight Decrease	<1	3
Cardiovascular Disorders, General		
Hypertension	2	3
Central and Peripheral Nervous System		
Dizziness	11	21
Headache	12	17
Somnolence	3	5
Tremor	1	4
Gastrointestinal System		
Nausea	12	47
Vomiting	6	31
Diarrhea	11	19
Anorexia	3	17
Abdominal Pain	6	13
Dyspepsia	4	9
Constipation	4	5
Flatulence	2	4
Eructation	1	2
Psychiatric Disorders		
Insomnia	7	9
Confusion	7	8
Depression	4	6
Anxiety	3	5
Hallucination	3	4
Aggressive Reaction	2	3
Resistance Mechanism Disorders		
Urinary Tract Infection	6	7
Respiratory System		
Rhinitis	3	4

Other adverse events observed at a rate of 2% or more on Exelon 6-12 mg/day but at a greater or equal rate on placebo were chest pain, peripheral edema, vertigo, back pain, arthralgia, pain, bone fracture, agitation, nervousness, delusion, paranoid reaction, upper respiratory tract infections, infection (general), coughing, pharyngitis, bronchitis, rash (general), urinary incontinence.

Other Adverse Events Observed During Clinical Trials: Exelon has been administered to over 5297 individuals during clinical trials worldwide. Of these, 4326 patients have been treated for at least 3 months, 3407 patients have been treated for at least 6 months, 2150 patients have been treated for 1 year, 1250 have been treated for 2 years, and 168 have been treated for over 3 years. With regard to exposure to the highest dose, 2809 patients were exposed to doses of 10-12 mg, 2615 patients treated for 3 months, 2328 patients treated for 6 months, 1378 patients treated for 1 year, 917 patients treated for 2 years, and 129 treated for over 3 years.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 9 open-label trials in North America, Western Europe, Australia, South Africa, and Japan were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified WHO dictionary, and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 5297 patients from these trials who experienced that event while receiving Exelon. All adverse events occurring in at least 6 patients (approximately 0.1%) are included, except for those already listed elsewhere in labeling, WHO terms too general to be informative, relatively minor events, or events unlikely to be drug caused. Events are classified by body system and listed using the following definitions: frequent adverse events – those occurring in at least 1/100 patients; infrequent adverse events – those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Exelon treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Autonomic Nervous System: *Infrequent:* Cold clammy skin, dry mouth, flushing, increased saliva.

Body as a Whole: *Frequent:* Accidental trauma, fever, edema, allergy, hot flushes, rigors. *Infrequent:* Edema periorbital or facial, hypothermia, edema, feeling cold, halitosis.

Cardiovascular System: *Frequent:* Hypotension, postural hypotension, cardiac failure.

Central and Peripheral Nervous System: *Frequent:* Abnormal gait, ataxia, paraesthesia, convulsions. *Infrequent:* Paresis, apraxia, aphasia, dysphonia, hyperkinesia, hyperreflexia, hypertonia, hypoesthesia, hypokinesia, migraine, neuralgia, nystagmus, peripheral neuropathy.

Endocrine System: *Infrequent:* Goitre, hypothyroidism.

Gastrointestinal System: *Frequent:* Fecal incontinence, gastritis. *Infrequent:* Dysphagia, esophagitis, gastric ulcer, gastritis, gastroesophageal reflux, GI hemorrhage, hernia, intestinal obstruction, melena, rectal hemorrhage, gastroenteritis, ulcerative stomatitis, duodenal ulcer, hematemesis, gingivitis, tenesmus, pancreatitis, colitis, glossitis.

Hearing and Vestibular Disorders: *Frequent:* Tinnitus.

Heart Rate and Rhythm Disorders: *Frequent:* Atrial fibrillation, bradycardia, palpitation. *Infrequent:* AV block, bundle branch block, sick sinus syndrome, cardiac arrest, supraventricular tachycardia, extrasystoles, tachycardia.

Liver and Biliary System Disorders: *Infrequent:* Abnormal hepatic function, cholecystitis.

Metabolic and Nutritional Disorders: *Frequent:* Dehydration, hypokalemia. *Infrequent:* Diabetes mellitus, gout, hypercholesterolemia, hyperlipemia, hypoglycemia, cachexia, thirst, hyperglycemia, hyponatremia.

Musculoskeletal Disorders: *Frequent:* Arthritis, leg cramps, myalgia. *Infrequent:* Cramps, hernia, muscle weakness.

Myo-, Endo-, Pericardial and Valve Disorders: *Frequent:* Angina pectoris, myocardial infarction.

Platelet, Bleeding, and Clotting Disorders: *Frequent:* Epistaxis. *Infrequent:* Hematoma, thrombocytopenia, purpura.

Psychiatric Disorders: *Frequent:* Paranoid reaction, confusion. *Infrequent:* Abnormal dreaming, amnesia, apathy, delirium, dementia, depersonalization, emotional lability, impaired concentration, decreased libido, personality disorder, suicide attempt, increased libido, neurosis, suicidal ideation, psychosis.

Red Blood Cell Disorders: *Frequent:* Anemia. *Infrequent:* Hypochromic anemia.

Reproductive Disorders (Female & Male): *Infrequent:* Breast pain, impotence, atrophic vaginitis.

Resistance Mechanism Disorders: *Infrequent:* Cellulitis, cystitis, herpes simplex, otitis media.

Respiratory System: *Infrequent:* Bronchospasm, laryngitis, apnea.

Skin and Appendages: *Frequent:* Rashes of various kinds (maculopapular, eczema, bullous, exfoliative, psoriaform, erythematous). *Infrequent:* Alopecia, skin ulceration, urticaria, dermatitis contact.

Special Senses: *Infrequent:* Perversion of taste, loss of taste.

Urinary System Disorders: *Frequent:* Hematuria. *Infrequent:* Albuminuria, oliguria, acute renal failure, dysuria, micturition urgency, nocturia, polyuria, renal calculus, urinary retention.

Vascular (extracardiac) Disorders: *Infrequent:* Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, thrombophlebitis deep, aneurysm, hemorrhage intracranial.

Vision Disorders: *Frequent:* Cataract. *Infrequent:* Conjunctival hemorrhage, blepharitis, diplopia, eye pain, glaucoma.

White Cell and Resistance Disorders: *Infrequent:* Lymphadenopathy, leukocytosis.

Post-Introduction Reports: Voluntary reports of adverse events temporally associated with Exelon that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:

Skin and Appendages: Stevens-Johnson syndrome.

Store below 77°F (25°C) in a tight container.

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Geriatrics®

Medicine for Midlife and Beyond

Geriatrics is a monthly peer-reviewed medical journal for primary care physicians and geriatricians. Its editorial mission is to publish evidence-based reviews, news, and other clinical information that these physicians can use in their practices today to provide quality care for midlife and older adults.

Articles published in Geriatrics are listed in Index Medicus and Current Contents. The editors of Geriatrics seek physician-authored clinical review articles relating to the health care of patients age 50 and older. Information for authors can be found on our web site at www.geri.com

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Geriatrics®
Medicine for Midlife and Beyond

Information for Authors

General information

Geriatrics is a peer-reviewed monthly clinical journal sent on request to 74,000 U.S. geriatricians and primary care physicians in office-based practice. It is also published in four international editions and is listed in *Index Medicus* and *Current Contents*.

The editors of Geriatrics seek previously unpublished review-style articles by MD or DO authors relating to the health care of patients age 50 and older. We do not publish original research. Manuscripts should be written in a conversational style and target the practical day-to-day needs of office-based primary care physicians with midlife and older patients.

At least one author must be of assistant professor ranking or higher. Resident, fellow, or instructor co-authors are welcome. Provide full name, complete mailing address, e-mail address, telephone and fax numbers, and principal academic titles or professional affiliations of every author.

Format

Acceptable manuscripts are typewritten, double-spaced, and limited to 2,000 words (8 to 10 pages). Include a 100- to 125-word abstract summarizing the main points of the article. Online submissions are preferred (aluddington@advanstar.com). Otherwise, submit an original and one copy of the article and all illustrative materials on paper and disk, preferrably in a version of Microsoft Word for PC or Macintosh.

References

Limit references to 20 citations. Cite references in the text in numerical sequence. Following AMA style, type references on a separate sheet and include (in order) full names of authors, complete title of article cited, abbreviated name of journal according to *Index Medicus*, year of publication, volume and issue numbers, and inclusive page numbers. For references to books, monographs and pamphlets, include full name of author(s), title, edition, location and name of publisher, year of publication, and inclusive page numbers.

Illustrative materials

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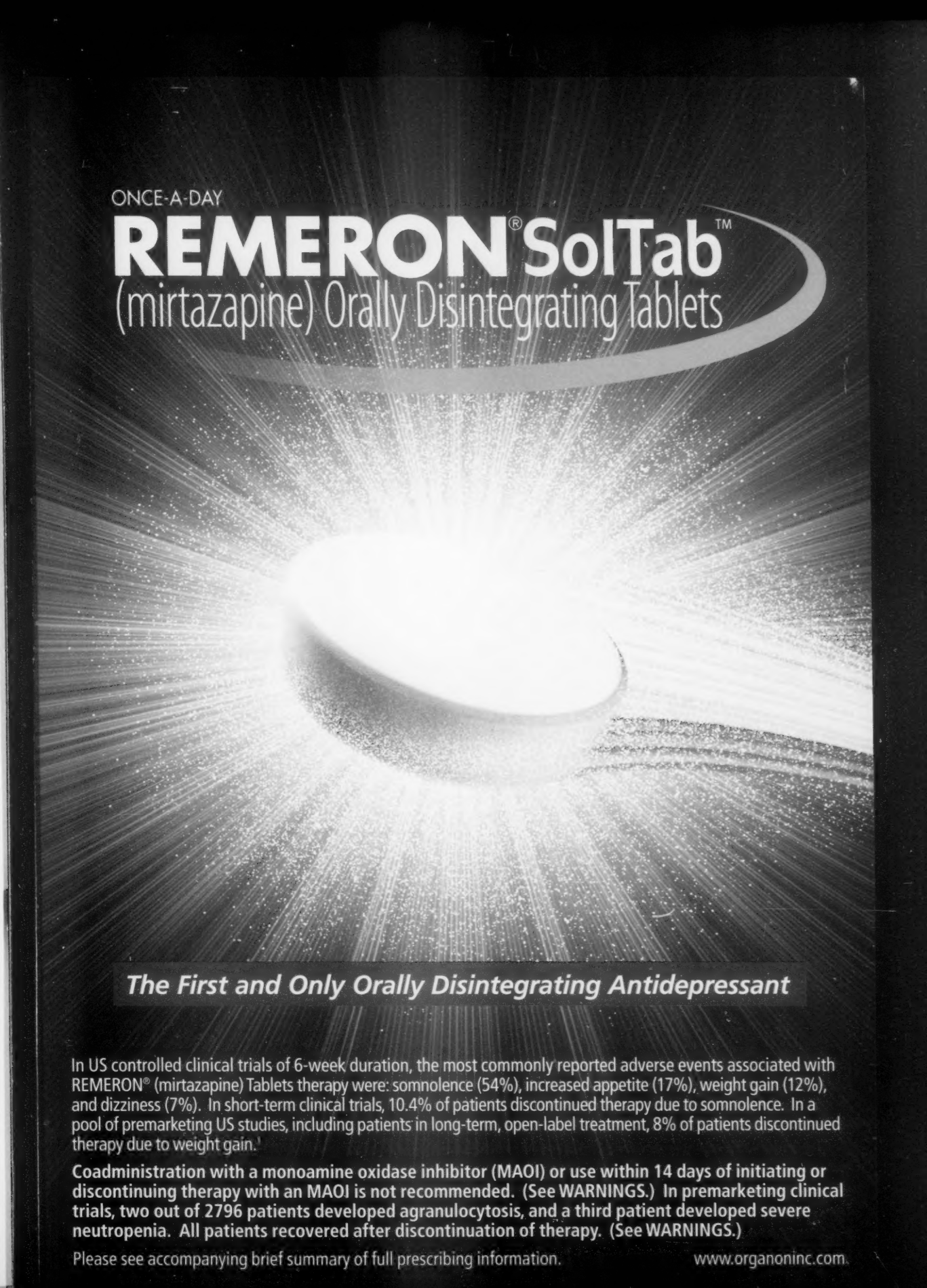

In US controlled clinical trials of 6-week duration, the most commonly reported adverse events associated with REMERON® (mirtazapine) Tablets therapy were: somnolence (54%), increased appetite (17%), weight gain (12%), and dizziness (7%). In short-term clinical trials, 10.4% of patients discontinued therapy due to somnolence. In a pool of premarketing US studies, including patients in long-term, open-label treatment, 8% of patients discontinued therapy due to weight gain.[1]

Coadministration with a monoamine oxidase inhibitor (MAOI) or use within 14 days of initiating or discontinuing therapy with an MAOI is not recommended. (See WARNINGS.) In premarketing clinical trials, two out of 2796 patients developed agranulocytosis, and a third patient developed severe neutropenia. All patients recovered after discontinuation of therapy. (See WARNINGS.)

Please see accompanying brief summary of full prescribing information.

www.organoninc.com

ONCE A DAY

REMERON® SolTab™

(mirtazapine) Orally Disintegrating Tablets

Before prescribing, please consult full prescribing information, a summary of which follows:

INDICATIONS AND USAGE: REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets are indicated for the treatment of depression.

CONTRAINDICATIONS: REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets are contraindicated in patients with a known hypersensitivity to mirtazapine.

WARNINGS: Agranulocytosis: In premarketing clinical trials, two (one with Sjögren's Syndrome) out of 2796 patients treated with REMERON® (mirtazapine) Tablets developed agranulocytosis (absolute neutrophil count (ANC) < 500/mm³ with associated signs and symptoms, e.g., fever, infection, etc.) and a third patient developed severe neutropenia (ANC < 500/mm³ without any associated symptoms). For these three patients, onset of severe neutropenia was detected on days 61, 9, and 14 of treatment, respectively. All three patients recovered after REMERON® was stopped. These three cases yield a crude incidence of severe neutropenia (with or without associated infection) of approximately 1.1 per thousand patients exposed, with a very wide 95% confidence interval, i.e., 2.2 cases per 10,000 to 3.1 cases per 1000. If a patient develops a sore throat, fever, stomatitis or other signs of infection, along with a low WBC count, treatment with REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets should be discontinued and the patient should be closely monitored. • MAO Inhibitors: In patients receiving other antidepressants in combination with a monoamine oxidase inhibitor (MAOI) and in patients who have recently discontinued an antidepressant drug and then are started on an MAOI, there have been reports of serious, and sometimes fatal, reactions, including nausea, vomiting, flushing, dizziness, tremor, myoclonus, rigidity, diaphoresis, hyperthermia, autonomic instability with rapid fluctuations of vital signs, seizures, and mental status changes ranging from agitation to coma. Although there are no human data pertinent to such an interaction with REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets, it is recommended that REMERON®SolTab™ not be used in combination with an MAOI, or within 14 days of initiating or discontinuing therapy with an MAOI.

PRECAUTIONS: General: Somnolence: In US controlled studies, somnolence was reported in 54% of patients treated with REMERON® (mirtazapine) Tablets, compared to 18% for placebo and 60% for amitriptyline. In these studies, somnolence resulted in discontinuation for 10.4% of REMERON® treated patients, compared to 2.2% for placebo. It is unclear whether or not tolerance develops to the somnolent effects of REMERON®. Because of REMERON®'s potentially significant effects on impairment of performance, patients should be cautioned about engaging in activities requiring alertness until they have been able to assess the drug's effect on their own psychomotor performance (see Information for Patients). • Dizziness: In US controlled studies, dizziness was reported in 7% of patients treated with REMERON®, compared to 3% for placebo and 14% for amitriptyline. It is unclear whether or not tolerance develops to the dizziness observed in association with the use of REMERON®. • Increased Appetite/Weight Gain: In US controlled studies, appetite increase was reported in 17% of patients treated with REMERON® compared to 2% for placebo and 6% for amitriptyline. In these same trials, weight gain of ≥ 7% of body weight was reported in 7.5% of patients treated with mirtazapine, compared to 0% for placebo and 5.9% for amitriptyline. In a pool of premarketing US studies, including many patients for long-term, open label treatment, 8% of patients receiving REMERON® discontinued for weight gain. • Cholesterol/Triglycerides: In US controlled studies, nonfasting cholesterol increases to ≥ 20% above the upper limits of normal were observed in 15% of patients treated with REMERON®, compared to 7% for placebo and 8% for amitriptyline. In these same studies, nonfasting triglyceride increases to ≥ 500 mg/dL were observed in 6% of patients treated with mirtazapine, compared to 3% for placebo and 3% for amitriptyline. • Transaminase Elevations: Clinically significant ALT (SGPT) elevations (≥ 3 times the upper limit of the normal range) were observed in 2.0% (8/424) of patients exposed to REMERON® in a pool of short-term US controlled trials, compared to 0.3% (1/328) of placebo patients and 2.0% (3/181) of amitriptyline patients. Most of these patients with ALT increases did not develop signs or symptoms associated with compromised liver function. While some patients were discontinued for the ALT increases, in other cases, the enzyme levels returned to normal despite continued REMERON® treatment. REMERON®SolTab™ should be used with caution in patients with impaired hepatic function (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). • Activation of Mania/Hypomania: Mania/hypomania occurred in approximately 0.2% (3/1299 patients) of REMERON®-treated patients in US studies. Although the incidence of mania/hypomania was very low during treatment with mirtazapine, it should be used carefully in patients with a history of mania/hypomania. • Seizure: In premarketing clinical trials only one seizure was reported among the 2796 US and non-US patients treated with REMERON®. However, no controlled studies have been carried out in patients with a history of seizures. Therefore, care should be exercised when mirtazapine is used in these patients. • Suicide: Suicidal ideation is inherent in depression and may persist until significant remission occurs. As with any patient receiving antidepressants, high-risk patients should be closely supervised during initial drug therapy. Prescriptions of REMERON®SolTab™ should be written for the smallest quantity consistent with good patient management, in order to reduce the risk of overdose. • Use in Patients with Concomitant Illness: Clinical experience with REMERON®SolTab™ in patients with concomitant systemic illness is limited. Accordingly, care is advisable in prescribing mirtazapine for patients with diseases or conditions that affect metabolism or hemodynamic responses. • REMERON®SolTab™ has not been systematically evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or other significant heart disease. REMERON® was associated with significant orthostatic hypotension in early clinical phapmacology trials with normal volunteers. Orthostatic hypotension was infrequently observed in clinical trials with depressed patients. REMERON®SolTab™ should be used with caution in patients with known cardiovascular or cerebrovascular disease that could be exacerbated by hypotension (history of myocardial infarction, angina, or ischemic stroke) and conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medication). • Mirtazapine clearance is decreased in patients with moderate [glomerular filtration rate (GFR) = 11–39 mL/min/1.73 m²] and severe [GFR < 10 mL/min/1.73 m²] renal impairment, and also in patients with hepatic impairment. Caution is indicated in administering REMERON®SolTab™ to such patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). • **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets: • Agranulocytosis: Patients who are to receive REMERON®SolTab™ should be warned about the risk of developing agranulocytosis. Patients should be advised to contact their physician if they experience any indication of infection such as fever, chills, sore throat, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection. • Interference with Cognitive and Motor Performance: REMERON®SolTab™ may impair judgement, thinking, and particularly motor skills, because of its prominent sedative effect. The drowsiness associated with mirtazapine use may impair a patient's ability to drive, use machines or perform tasks that require alertness. Thus, patients should be cautioned about engaging in hazardous activities until they are reasonably certain that REMERON®SolTab™ therapy does not adversely affect their ability to engage in such activities. • Completing Course of Therapy: While patients may notice improvement with REMERON®SolTab™ therapy in 1 to 4 weeks, they should be advised to continue therapy as directed. • Concomitant Medication: Patients should be advised to inform their physician if they are taking, or intend to take, any prescription or over-the-counter drugs since there is a potential for REMERON®SolTab™ to interact with other drugs. • Alcohol: The impairment of cognitive and motor skills produced by REMERON® has been shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking any dosage form of mirtazapine. • Phenylketonurics: Phenylketonuric patients should be informed that REMERON®SolTab™ contains phenylalanine 2.6 mg per 15 mg tablet, 5.2 mg per 30 mg tablet, and 7.8 mg per 45 mg tablet. • Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during REMERON®SolTab™ therapy. • Nursing: Patients should be advised to notify their physician if they are breast-feeding an infant. • **Laboratory Tests:** There are no routine laboratory tests recommended. • **Drug Interactions:** As with other drugs, the potential for interaction by a variety of mechanisms (e.g., pharmacodynamic, pharmacokinetic inhibition or enhancement, etc.) is a possibility (see CLINICAL PHARMACOLOGY). • Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets may be affected by the induction or inhibition of drug-metabolizing enzymes. • Drugs that are Metabolized by and/or Inhibit Cytochrome P450 Enzymes: Many drugs are metabolized by and/or inhibit various cytochrome P450 enzymes, e.g., 2D6, 1A2, 3A4, etc. *In vitro* studies have shown that mirtazapine is a substrate for several of these enzymes, including 2D6, 1A2, and 3A4. While *in vitro* studies have shown that mirtazapine is not a potent inhibitor of any of these enzymes, an indication that mirtazapine is not likely to have a clinically significant inhibitory effect on the metabolism of other drugs that are substrates for these cytochrome P450 enzymes, the concomitant use of REMERON®SolTab™ with most other drugs metabolized by these enzymes has not been formally studied. Consequently, it is not possible to make any definitive statements about the risks of coadministration of REMERON®SolTab™ with such drugs. • Alcohol: Concomitant administration of alcohol (equivalent to 60 g) had a minimal effect on plasma levels of mirtazapine (15 mg) in 6 healthy male subjects. However, the impairment of cognitive and motor skills produced by REMERON® were shown to be additive with those produced by alcohol. Accordingly, patients should be advised to avoid alcohol while taking REMERON®SolTab™. • Diazepam: Concomitant administration of diazepam (15 mg) had a minimal effect on plasma levels of mirtazapine (15 mg) in 12 healthy subjects. However, the impairment of motor skills produced by REMERON® has been shown to be additive with those caused by diazepam. Accordingly, patients should be advised to avoid diazepam and other similar drugs while taking REMERON®SolTab™.

• Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Carcinogenicity studies were conducted with mirtazapine given in the diet at doses of 2, 20, and 200 mg/kg/day to mice and 2, 20, and 60 mg/kg/day to rats. The highest doses used are approximately 20 and 12 times the maximum recommended human dose (MRHD) of 45 mg/day on a mg/m² basis in mice and rats, respectively. There was an increased incidence of hepatocellular adenoma and carcinoma in male mice at the high dose. In rats, there was an increase in hepatocellular adenoma in females at the mid and high doses and in hepatocellular tumors and thyroid follicular adenoma/cystadenoma and carcinoma in males at the high dose. The data suggest that the above effects could possibly be mediated by non-genotoxic mechanisms, the relevance of which to humans is not known. • The doses used in the mouse study may not have been high enough to fully characterize the carcinogenic potential of REMERON® (mirtazapine) Tablets. • Mutagenesis: Mirtazapine was not mutagenic or clastogenic and did not induce general DNA damage as determined in several genotoxicity tests: Ames test; *in vitro* gene mutation assay in Chinese hamster V 79 cells; *in vitro* sister chromatid exchange assay in cultured rabbit lymphocytes; *in vivo* bone marrow micronucleus test in rats; and unscheduled DNA synthesis assay in HeLa cells. • Impairment of Fertility: In a fertility study in rats, mirtazapine was given at doses up to 100 mg/kg [20 times the maximum recommended human dose (MRHD) on a mg/m² basis]. Mating and conception were not affected by the drug, but estrous cycling was disrupted at doses that were 3 or more times the MRHD and pre-implantation losses occurred at 20 times the MRHD. • **Pregnancy:** Teratogenic Effects – Pregnancy Category C: Reproduction studies in pregnant rats and rabbits at doses up to 100 mg/kg and 40 mg/kg, respectively [20 and 17 times the maximum recommended human dose (MRHD) on a mg/m² basis, respectively], have revealed no evidence of teratogenic effects. However, in rats, there was an increase in post-implantation losses in dams treated with mirtazapine. There was an increase in pup deaths during the first 3 days of lactation and a decrease in pup birth weights. The cause of these deaths is not known. The effects occurred at doses that were 20 times the MRHD, but not at 3 times the MRHD, on a mg/m² basis. There are no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. • **Nursing Mothers:** It is not known whether mirtazapine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets are administered to nursing women. • **Pediatric Use:** Safety and effectiveness in children have not been established. • **Geriatric Use:** Approximately 190 elderly individuals (≥ 65 years of age) participated in clinical studies with REMERON® (mirtazapine) Tablets. This drug is known to be substantially excreted by the kidney (75%), and the risk of decreased clearance of this drug is greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Sedating drugs may cause confusion and over-sedation in the elderly. No unusual adverse age-related phenomena were identified in this group. Pharmacokinetic studies revealed a decreased clearance in the elderly. Caution is indicated in administering REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets to elderly patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS: Associated with Discontinuation of Treatment: Approximately 16 percent of the 453 patients who received REMERON® (mirtazapine) Tablets in US 6-week controlled clinical trials discontinued treatment due to an adverse experience, compared to 7 percent of the 361 placebo-treated patients in those studies. The most common events (≥ 1%) associated with discontinuation and considered to be drug related (i.e., those events associated with dropout at a rate at least twice that of placebo) included:

Common Adverse Events Associated with Discontinuation of Treatment in 6-Week US REMERON® Trials		
Adverse Event	Percentage of Patients Discontinuing with Adverse Event	
	REMERON® (n=453)	Placebo (n=361)
Somnolence	10.4%	2.2%
Nausea	1.5%	0%

Commonly Observed Adverse Events in US Controlled Clinical Trials: The most commonly observed adverse events associated with the use of REMERON® (mirtazapine) Tablets (incidence of 5% or greater) and not observed at an equivalent incidence among placebo-treated patients (REMERON® incidence at least twice that for placebo) were:

Common Treatment-Emergent Adverse Events Associated with the Use of REMERON® in 6-Week US Trials		
Adverse Event	Percentage of Patients Reporting Adverse Event	
	REMERON® (n=453)	Placebo (n=361)
Somnolence	54%	18%
Increased Appetite	17%	2%
Weight Gain	12%	2%
Dizziness	7%	3%

Adverse Events Occurring at an Incidence of 1% or More Among REMERON®-Treated Patients: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among REMERON® (mirtazapine) Tablets-treated patients who participated in short-term US placebo-controlled trials in which patients were dosed in a range of 5 to 60 mg/day. This table shows the percentage of patients in each group who had at least one episode of an event at some time during their treatment. Reported adverse events were classified using a standard COSTART-based dictionary terminology. • The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied.

INCIDENCE OF ADVERSE CLINICAL EXPERIENCES[1] (≥ 1%) IN SHORT-TERM US CONTROLLED STUDIES

Body System Adverse Clinical Experience	REMERON® (n=453)	Placebo (n=361)
Body as a Whole		
Asthenia	8%	5%
Flu Syndrome	5%	3%
Back Pain	2%	1%
Digestive System		
Dry Mouth	25%	15%
Increased Appetite	17%	2%
Constipation	13%	7%
Metabolic and Nutritional Disorders		
Weight Gain	12%	2%
Peripheral Edema	2%	1%
Edema	1%	0%
Musculoskeletal System		
Myalgia	2%	1%
Nervous System		
Somnolence	54%	18%
Dizziness	7%	3%
Abnormal Dreams	4%	1%
Thinking Abnormal	3%	1%
Tremor	2%	1%
Confusion	2%	0%
Respiratory System		
Dyspnea	1%	0%
Urogenital System		
Urinary Frequency	2%	1%

[1] Events reported by at least 1% of patients treated with REMERON® are included, except the following events which had an incidence on placebo ≥ REMERON®: headache, infection, pain, chest pain, palpitation, tachycardia, postural hypotension, nausea, dyspepsia, diarrhea, flatulence, insomnia, nervousness, libido decreased, hypertonia, pharyngitis, rhinitis, sweating, amblyopia, tinnitus, taste perversion.

ECG Changes: The electrocardiograms for 338 patients who received REMERON® and 261 patients who received placebo in 6-week placebo-controlled trials were analyzed. Prolongation in QTc ≥ 500 msec was not observed among mirtazapine-treated patients; mean change in QTc was +1.6 msec for mirtazapine and –3.1 msec for placebo. Mirtazapine was associated with a mean increase in heart rate of 3.4 bpm, compared to 0.8 bpm for placebo. The clinical significance of these changes is unknown.

• Other Adverse Events Observed During the Premarketing Evaluation of REMERON®: During its premarketing assessment, multiple doses of REMERON® (mirtazapine) Tablets were administered to 2796 patients in clinical studies. The conditions and duration of exposure to mirtazapine varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. • In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2796 patients exposed to multiple doses of REMERON® who experienced an event of the type cited on at least one occasion while receiving REMERON®. All reported events are included except those already listed in the previous table, those adverse experiences subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, and those events for which a drug cause was very remote. • It is important to emphasize that, although the events reported occurred during treatment with REMERON®, they were not necessarily caused by it. • Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Only those events not already listed in the previous table appear in this listing. Events of major clinical importance are also described in the WARNINGS and PRECAUTIONS sections. • Body as a Whole: *frequent*: malaise, abdominal pain, abdominal syndrome acute; *infrequent*: chills, fever, face edema, ulcer, photosensitivity reaction, neck rigidity, neck pain, abdomen enlarged; *rare*: cellulitis, chest pain substernal. • Cardiovascular System: *frequent*: hypertension, vasodilatation; *infrequent*: angina pectoris, myocardial infarction, bradycardia, ventricular extrasystoles, syncope, migraine, hypotension; *rare*: atrial arrhythmia, bigeminy, vascular headache, pulmonary embolus, cerebral ischemia, cardiomegaly, phlebitis, left heart failure. • Digestive System: *frequent*: vomiting, anorexia; *infrequent*: eructation, glossitis, cholecystitis, nausea and vomiting, gum hemorrhage, stomatitis, colitis, liver function tests abnormal; *rare*: tongue discoloration, ulcerative stomatitis, salivary gland enlargement, increased salivation, intestinal obstruction, pancreatitis, aphthous stomatitis, cirrhosis of liver, gastritis, gastroenteritis, oral moniliasis, tongue edema. • Endocrine System: *rare*: goiter, hypothyroidism. • Hemic and Lymphatic System: *rare*: lymphadenopathy, leukopenia, petechia, anemia, thrombocytopenia, lymphocytosis, pancytopenia. • Metabolic and Nutritional Disorders: *frequent*: thirst; *infrequent*: dehydration, weight loss; *rare*: gout, SGOT increased, healing abnormal, acid phosphatase increased, SGPT increased, diabetes mellitus. • Musculoskeletal System: *frequent*: myasthenia, arthralgia; *infrequent*: arthritis, tenosynovitis; *rare*: pathological fracture, osteoporosis fracture, bone pain, myositis, tendon rupture, arthrosis, bursitis. • Nervous System: *frequent*: hypesthesia, apathy, depression, hypokinesia, vertigo, twitching, agitation, anxiety, amnesia, hyperkinesia, paresthesia; *infrequent*: ataxia, delirium, delusions, depersonalization, dyskinesia, extrapyramidal syndrome, libido increased, coordination abnormal, dysarthria, hallucinations, manic reaction, neurosis, dystonia, hostility, reflexes increased, emotional lability, euphoria, paranoid reaction; *rare*: aphasia, nystagmus, akathisia, stupor, dementia, diplopia, drug dependence, paralysis, grand mal convulsion, hypotonia, myoclonus, psychotic depression, withdrawal syndrome. • Respiratory System: *frequent*: cough increased, sinusitis; *infrequent*: epistaxis, bronchitis, asthma, pneumonia; *rare*: asphyxia, laryngitis, pneumothorax, hiccup. • Skin and Appendages: *frequent*: pruritus, rash; *infrequent*: acne, exfoliative dermatitis, dry skin, herpes simplex, alopecia; *rare*: urticaria, herpes zoster, skin hypertrophy, seborrhea, skin ulcer. • Special Senses: *infrequent*: eye pain, abnormality of accommodation, conjunctivitis, deafness, keratoconjunctivitis, lacrimation disorder, glaucoma, hyperacusis, ear pain; *rare*: blepharitis, partial transitory deafness, otitis media, taste loss, parosmia. • Urogenital System: *frequent*: urinary tract infection; *infrequent*: kidney calculus, cystitis, dysuria, urinary incontinence, urinary retention, vaginitis, hematuria, breast pain, amenorrhea, dysmenorrhea, leukorrhea, impotence; *rare*: polyuria, urethritis, metrorrhagia, menorrhagia, abnormal ejaculation, breast engorgement, breast enlargement, urinary urgency. • **Other Adverse Events Observed During Postmarketing Evaluation of REMERON®:** Adverse events reported since market introduction, which were temporally (but not necessarily causally) related to mirtazapine therapy, include four cases of the ventricular arrhythmia torsades de pointes. In three of the four cases, however, concomitant drugs were implicated. All patients recovered.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets are not a controlled substance. • **Physical and Psychologic Dependence:** REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets have not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of REMERON®SolTab™ misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE: Human Experience: There is very limited experience with REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets overdose. In premarketing clinical studies, there were eight reports of REMERON® overdose alone or in combination with other pharmacological agents. The only drug overdose death reported while taking REMERON® was in combination with amitriptyline and chlorprothixene in a non-US clinical study. Based on plasma levels, the REMERON® dose taken was 30–45 mg, while plasma levels of amitriptyline and chlorprothixene were found to be at toxic levels. All other premarketing overdose cases resulted in full recovery. Signs and symptoms reported in association with overdose included disorientation, drowsiness, impaired memory, and tachycardia. There were no reports of ECG abnormalities, coma or convulsions following overdose with REMERON® alone. • **Overdose Management:** Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients. Because of the rapid disintegration of REMERON®SolTab™ (mirtazapine) Orally Disintegrating Tablets, pill fragments may not appear in gastric contents obtained with lavage. • Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion or exchange transfusion in the treatment of mirtazapine overdosage. No specific antidotes for mirtazapine are known. • In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION: Storage: Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from light and moisture. Use immediately upon opening individual tablet blister.

℞ only

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REFERENCE:

1. Data on file, Organon Inc.

Organon
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AUGUST 2001

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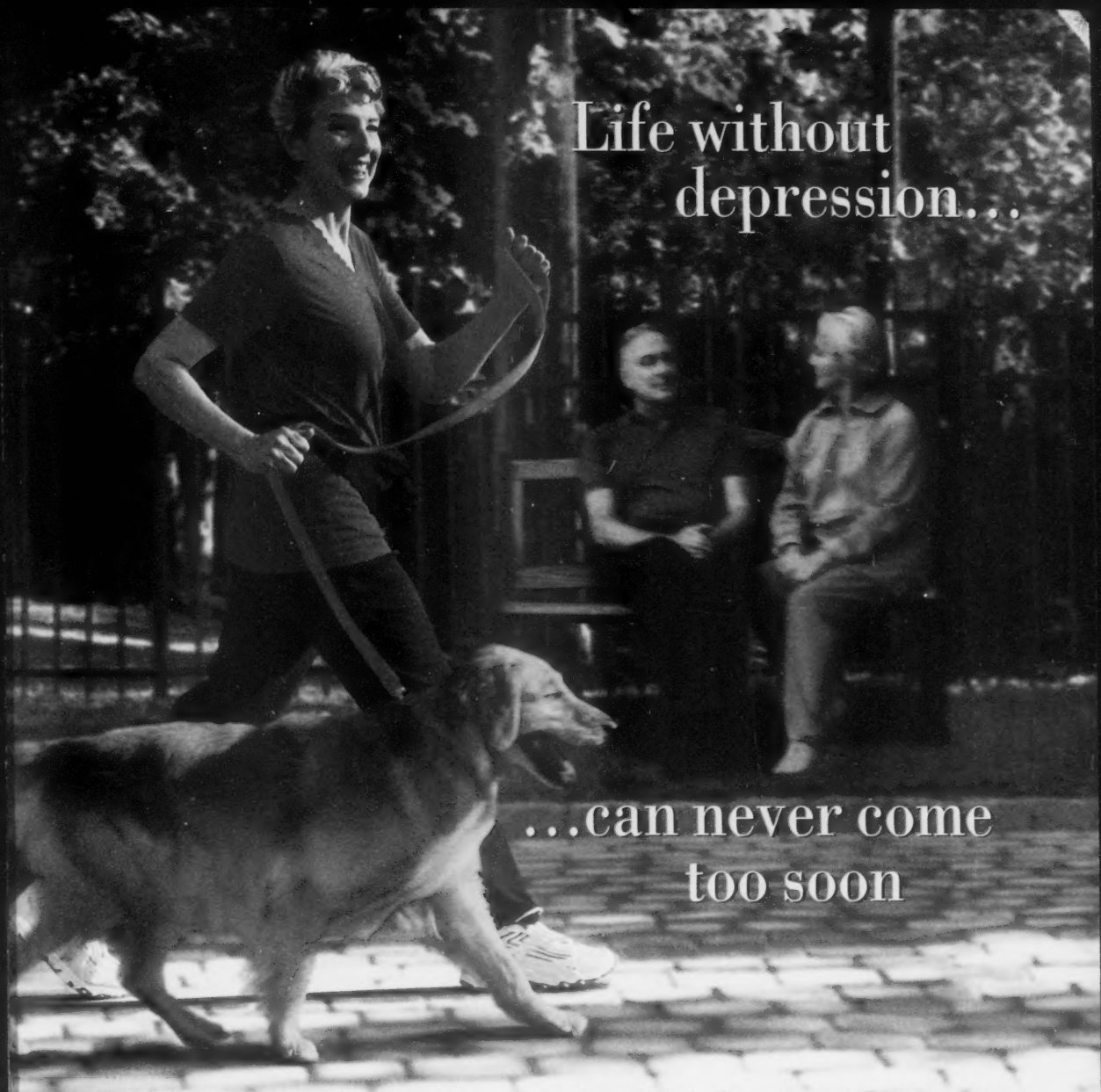

In US controlled clinical trials of 6-week duration, the most commonly reported adverse events associated with REMERON® (mirtazapine) Tablets therapy were: somnolence (54%), increased appetite (17%), weight gain (12%), and dizziness (7%). In short-term clinical trials, 10.4% of patients discontinued therapy due to somnolence. In a pool of premarketing US studies, including patients in long-term, open-label treatment, 8% of patients discontinued therapy due to weight gain.[1]

Coadministration with a monoamine oxidase inhibitor (MAOI) or use within 14 days of initiating or discontinuing therapy with an MAOI is not recommended. (See WARNINGS.) In premarketing clinical trials, two out of 2796 patients developed agranulocytosis, and a third patient developed severe neutropenia. All patients recovered after discontinuation of therapy. (See WARNINGS.)

ONCE-A-DAY

REMERON® SolTab™

(mirtazapine) Orally Disintegrating Tablets

Please see accompanying brief summary of full prescribing information.

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Results to believe in.

News Pulse

Monitoring research and trends in clinical care

New guidelines emphasize prevention of heart failure progression

Source: Journal of the American College of Cardiology, December and Circulation, December 11, 2001

A classification system that focuses on the evolution and progression of heart failure has been developed by the American College of Cardiology (ACC) and the American Heart Association (AHA) to complement the New York Heart Association (NYHA) functional class system. The heart failure classification system is part of new ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult.

The purpose of the new guidelines, and specifically the classification system, is to emphasize the importance of preventing heart failure in high-risk patients before they develop symptoms, said guideline committee chair Sharon A. Hunt, MD.

The classification system is divided into four stages of heart failure:

- Stage A: Patients at high risk for developing heart failure but are asymptomatic and do not have structural heart damage
- Stage B: Patients who are asymptomatic but have heart damage
- Stage C: Patients who have past or current symptoms of heart failure and have heart damage
- Stage D: Patients with end-stage disease.

Unlike NYHA functional class stages, which can change depending on whether or not a patient's function improves with treatment, the stages of the heart failure classification system progress, Dr. Hunt told Geriatrics. For example, once patients progress from stage B to C, they are classified under stage C even if treatment alleviates their symptoms.

"The reason for this [method of classifying patients] is that there are different forms of therapy that are appropriate at the different stages," said Dr. Hunt, professor of cardiovascular medicine, Stanford University.

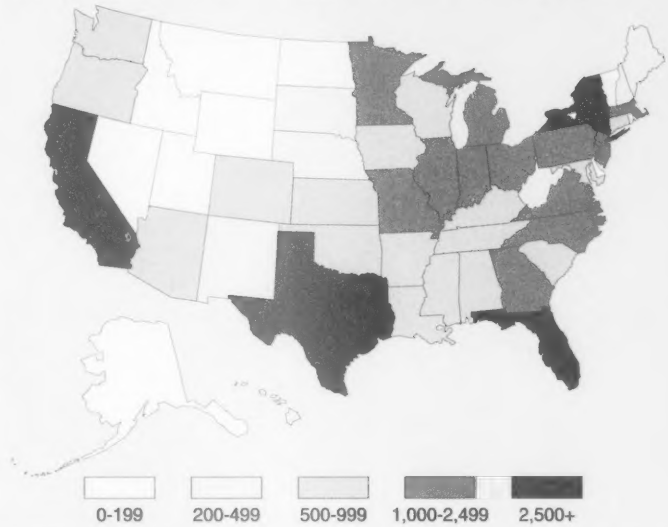
- For stage-A patients, therapy includes treatment for hypertension and lipid disorders, smoking cessation, regular exercise, therapy for alcohol abuse and illicit drug use, and treatment with angiotensin-converting enzyme (ACE) inhibitors if appropriate.
- For stage-B patients, therapy includes all methods recommended for stage A as well as treatment with beta blockers if appropriate.
- For stage-C patients, therapy includes all of the methods recommended for stage A as well as routine use of diuretics, ACE inhibitors, beta blockers, or digitalis plus dietary salt restrictions.
- For stage-D patients, therapy includes all of the methods for stages A, B, and C, as well as mechanical assist devices, heart transplantation, continuous IV inotropic infusions for palliation, and hospice care.

"The message behind the staging system is to make physicians aware of the preventable nature of heart failure and the need to employ appropriate therapies early," Dr. Hunt said.

continued

Clinicians' Corner

Population of Americans age 100 and older by state



The population of Americans age 100+ totaled 50,454 last year, according to a 2000 census report. They comprise <1% of the total 281.4 million U.S. population.

Source: U.S. Census Bureau, Census 2000 summary file 1; http://www.census.gov.

OxyContin® C II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

WARNING:

OxyContin® is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin® in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion.

OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin® Tablets are NOT intended for use as a prn analgesic.

OxyContin® 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin® TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OxyContin® TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

PURDUE

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OxyContin® II

(OXYCODONE HCl CONTROLLED-RELEASE) TABLETS

10 mg 20 mg 40 mg 80 mg* 160 mg*

*80 mg and 160 mg for use in opioid-tolerant patients only

WARNING:

OxyContin is an opioid agonist and a Schedule II controlled substance with an abuse liability similar to morphine.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

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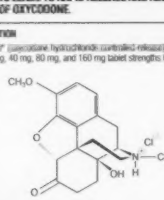
OxyContin TABLETS ARE TO BE SWALLOWED WHOLE AND ARE NOT TO BE BROKEN, CHEWED, OR CRUSHED. TAKING BROKEN, CHEWED, OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

DESCRIPTION

OxyContin® (oxycodone hydrochloride controlled-release) Tablets are an opioid analgesic supplied in 10 mg, 20 mg, 40 mg, 80 mg, and 160 mg tablet strengths for oral administration.



INDICATIONS AND USAGE

OxyContin® Tablets are a controlled-release oral formulation of oxycodone hydrochloride indicated for the management of moderate to severe pain when a continuous, around-the-clock analgesic is needed for an extended period of time.

OxyContin is **NOT** intended for use as a prn analgesic.

Physicians should individualize treatment in every case, initiating therapy at the appropriate point along a progression from non-opioid analgesics, such as non-steroidal anti-inflammatory drugs and acetaminophen to opioids in a plan of pain management such as outlined by the World Health Organization, the Agency for Healthcare Research and Quality (formerly known as the Agency for Health Care Policy and Research), the Federation of State Medical Boards Model Guidelines, or the American Pain Society.

OxyContin is not indicated for pain in the immediate postoperative period (the first 12-24 hours following surgery), or if the pain is mild, or not expected to persist for an extended period of time. OxyContin is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate. (See American Pain Society guidelines.)

CONTRAINDICATIONS

OxyContin® is contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercarbia. OxyContin is contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

DO NOT CRUSH, CHEW, BREAK, OR DISSOLVE OxyContin TABLETS. TAKING BROKEN, CHEWED OR CRUSHED OxyContin TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OXYCONTIN TABLETS ARE TO BE SWALLOWED WHOLE, AND ARE NOT TO BE BROKEN, CHEWED OR CRUSHED. TAKING BROKEN, CHEWED OR CRUSHED OXYCONTIN TABLETS LEADS TO RAPID RELEASE AND ABSORPTION OF A POTENTIALLY FATAL DOSE OF OXYCODONE.

OxyContin 80 mg and 160 mg Tablets ARE FOR USE IN OPIOID-TOLERANT PATIENTS ONLY. These tablet strengths may cause fatal respiratory depression when administered to patients not previously exposed to opioids.

OxyContin 80 mg and 160 mg Tablets are for use only in opioid-tolerant patients requiring daily oxycodone equivalent dosages of 160 mg or more for the 80 mg tablet and 320 mg or more for the 160 mg tablet. Care should be taken in the prescribing of these tablet strengths. Patients should be instructed against use by individuals other than the patient for whom it was prescribed, as such inappropriate use may have severe medical consequences, including death.

Misuse, Abuse and Diversion of Opioids

Oxycodone is an opioid agonist of the morphine-type. Such drugs are sought by drug abusers and people with addiction disorders and are subject to criminal diversion.

Oxycodone can be abused in a manner similar to other opioid agonists, legal or illicit. This should be considered when prescribing or dispensing OxyContin in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse, or diversion.

OxyContin has been reported as being abused by crushing, chewing, snorting, or injecting the dissolved product. These practices will result in the uncontrolled delivery of the opioid and pose a significant risk to the abuser that could result in overdose and death (see **WARNINGS** and **DRUG ABUSE AND ADDICTION**).

Concerns about abuse, addiction, and diversion should not prevent the proper management of pain. The development of addiction to opioid analgesics in properly managed patients with pain has been reported to be rare. However, data are not available to establish the true incidence of addiction in chronic pain patients.

Healthcare professionals should contact their State Professional Licensing Board, or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Interactions with Alcohol and Drugs of Abuse

Oxycodone may be expected to have additive effects when used in conjunction with alcohol, other opioids, or illicit drugs that cause central nervous system depression.

DRUG ABUSE AND ADDICTION

OxyContin® is a mu-agonist opioid with an abuse liability similar to morphine and is a Schedule II controlled substance. Oxycodone, like morphine and other opioids used in analgesia, can be abused and is subject to criminal diversion.

Drug addiction is characterized by compulsive use, use for non-medical purposes, and continued use despite harm or risk of harm. Drug addiction is a treatable disease, utilizing a multi-disciplinary approach, but relapse is common.

"Drug-seeking" behavior is very common in addicts and drug abusers. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating physician(s). "Doctor shopping" to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Physicians should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances. OxyContin®, like other opioids, has been diverted for non-medical use. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

OxyContin consists of a dual-polymer matrix, intended for oral use only. Abuse of the crushed tablet poses a hazard of overdose and death. This risk is increased with concurrent abuse of alcohol and other substances. With parenteral abuse, the tablet excipients, especially talc, can be expected to result in local tissue necrosis, infection, pulmonary granulomas, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Respiratory Depression

Respiratory depression is the chief hazard from oxycodone, the active ingredient in OxyContin®, as with all opioid agonists. Respiratory depression is a particular problem in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Head Injury

The respiratory depressant effects of opioids include carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure, and may be markedly exaggerated in the presence of head injury, intracranial lesions, or other sources of pre-existing increased intracranial pressure. Oxycodone produces effects on pupillary response and consciousness which may obscure neurologic signs of further increases in intracranial pressure in patients with head injuries.

Hypotensive Effect

OxyContin may cause severe hypotension. There is an added risk to individuals whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or other agents which compromise vasomotor tone. Oxycodone may produce orthostatic hypotension in ambulatory patients. Oxycodone, like all opioid analgesics of the morphine-type, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

PRECAUTIONS

General

Opioid analgesics have a narrow therapeutic index in certain patient populations, especially when combined with CNS depressant drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyContin® is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism; adrenocortical insufficiency (e.g., Addison's disease); CNS depression or coma; delirium tremens; debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary or renal function; and toxic psychosis.

The administration of oxycodone may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with other CNS Depressants

OxyContin should be used with caution and started in a reduced dosage (⅓ to ½ of the usual dosage) in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics; general anesthetics, phenothiazines, tranquilizers and alcohol. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with the usual doses of OxyContin.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

Agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Ambulatory Surgery and Postoperative Use

OxyContin is not indicated for pre-emptive analgesia (administration pre-operatively for the management of postoperative pain).

OxyContin is not indicated for pain in the immediate postoperative period (the first 12 to 24 hours following surgery) **for patients not previously taking the drug, because its safety in this setting has not been established.**

OxyContin is not indicated for pain in the postoperative period if the pain is mild or not expected to persist for an extended period of time.

OxyContin® is only indicated for postoperative use if the patient is already receiving the drug prior to surgery or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time. Physicians should individualize treatment, moving from parenteral to oral analgesics as appropriate (See American Pain Society guidelines).

Patients who are already receiving OxyContin® Tablets as part of ongoing analgesic therapy may be safely continued on the drug if appropriate dosage adjustments are made considering the procedure, other drugs given, and the temporary changes in physiology caused by the surgical intervention (see **DOSAGE AND ADMINISTRATION**).

OxyContin and other morphine-like opioids have been shown to decrease bowel motility. Ileus is a common postoperative complication, especially after intra-abdominal surgery with opioid analgesia. Caution should be taken to monitor for decreased bowel motility in postoperative patients receiving opioids. Standard supportive therapy should be implemented.

Use in Pancreatic/Biliary Tract Disease

Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

Tolerance and Physical Dependence

Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Physical dependence is manifested by withdrawal symptoms after abrupt discontinuation of a drug or upon administration of an antagonist. Physical dependence and tolerance are not unusual during chronic opioid therapy.

The opioid abstinence or withdrawal syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

In general, opioids should not be abruptly discontinued.

Information for Patients/Caregivers

If clinically advisable, patients receiving OxyContin Tablets or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be aware that OxyContin Tablets contain oxycodone, which is a morphine-like substance.
2. Patients should be advised that OxyContin Tablets were designed to work properly only if swallowed whole. OxyContin Tablets will release all their contents at once if broken, chewed, or crushed, resulting in a risk of fatal overdose.
3. Patients should be advised to report episodes of breakthrough pain and adverse experiences occurring during therapy. Individualization of dosage is essential to make optimal use of this medication.
4. Patients should be advised not to adjust the dose of OxyContin® without consulting the prescribing professional.
5. Patients should be advised that OxyContin may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
6. Patients should not combine OxyContin with alcohol or other central nervous system-depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because dangerous additive effects may occur, resulting in serious injury or death.
7. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
8. Patients should be advised that OxyContin is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
9. Patients should be advised that they may pass empty matrix 'ghosts' (tablets) via colostomy or in the stool, and that this is of no concern since the active medication has already been absorbed.
10. Patients should be advised that if they have been receiving treatment with OxyContin for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper the OxyContin dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.
11. Patients should be instructed to keep OxyContin in a secure place out of the reach of children. When OxyContin is no longer needed, the unused tablets should be destroyed by flushing down the toilet.

Use in Drug and Alcohol Addiction

OxyContin is an opioid with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions

Opioid analgesics, including OxyContin®, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxymorphone via cytochrome P450 2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs including amiodarone and quinidine as well as psychotic antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Use with CNS Depressants

OxyContin®, like all opioid analgesics, should be started at ⅓ to ½ of the usual dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, centrally acting anti-emetics, tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result. No specific interaction between oxycodone and monoamine oxidase inhibitors has been observed, but caution in the use of any opioid in patients taking this class of drugs is appropriate.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies of oxycodone to evaluate its carcinogenic potential have not been conducted.

Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. coli test with and without metabolic activation at doses of up to 5000 µg, chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the in vivo bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Oxycodone was clastogenic in the human lymphocyte chromosomal assay in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation.

Pregnancy

Teratogenic Effects — Category B: Reproduction studies have been performed in rats and rabbits by oral administration of doses up to 6 mg/kg and 125 mg/kg, respectively. These doses are 3 and 46 times a human dose of 160 mg/day, based on mg/kg basis. The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

OxyContin® is not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn. Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Nursing Mothers

Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyContin because of the possibility of sedation and/or respiratory depression in the infant.

Pediatric Use

Safety and effectiveness of OxyContin have not been established in pediatric patients below the age of 18. **It must be remembered that OxyContin Tablets cannot be crushed or divided for administration.**

Geriatric Use

In controlled pharmacokinetic studies in elderly subjects (greater than 65 years) the clearance of oxycodone appeared to be slightly reduced. Compared to young adults, the plasma concentrations of oxycodone were increased approximately 15%. Of the total number of subjects (445) in clinical studies of OxyContin, 148 (33.3%) were age 65 and older (including those age 75 and older) while 40 (9.0%) were age 75 and older. In clinical trials with appropriate initiation of therapy and dose titration, no untoward or unexpected side effects were seen in the elderly patients who received OxyContin. Thus, the usual doses and dosing intervals are appropriate for these patients. As with all opioids, the starting dose should be reduced to ⅓ to ½ of the usual dosage in debilitated, non-tolerant patients. Respiratory depression is the chief hazard in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Laboratory Monitoring

Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual or complex cases.

Hepatic Impairment

A study of OxyContin in patients with hepatic impairment indicates greater plasma concentrations than those with normal function. The initiation of therapy at ⅓ to ½ the usual doses and careful dose titration is warranted.

Renal Impairment

In patients with renal impairment, as evidenced by decreased creatinine clearance (<60 mL/min), the concentrations of oxycodone in the plasma are approximately 50% higher than in subjects with normal renal function. Dose initiation should follow a conservative approach. Dosages should be adjusted according to the clinical situation.

Gender Differences

In pharmacokinetic studies, opioid-naive females demonstrate up to 25% higher average plasma concentrations and greater frequency of typical opioid adverse events than males, even after adjustment for body weight. The clinical relevance of a difference of this magnitude is low for a drug intended for chronic usage at individualized dosages, and there was no male/female difference detected for efficacy or adverse events in clinical trials.

ADVERSE REACTIONS

The safety of OxyContin® was evaluated in double-blind clinical trials involving 713 patients with moderate to severe pain of various etiologies. In open-label studies of cancer pain, 887 patients received OxyContin in total daily doses ranging from 20 mg to 640 mg per day. The average total daily dose was approximately 105 mg per day.

Serious adverse reactions which may be associated with OxyContin Tablet therapy in clinical use are those observed with other opioid analgesics, including respiratory depression, apnea, respiratory arrest, and (to an even lesser degree) circulatory depression, hypotension, or shock (see **OVERDOSAGE**).

The non-serious adverse events seen on initiation of therapy with OxyContin are typical opioid side effects. These events are dose-dependent, and their frequency depends upon the dose, the clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. They should be expected and managed as a part of opioid analgesia. The most frequent (>5%) include: constipation, nausea, somnolence, dizziness, vomiting, pruritus, headache, dry mouth, sweating, and asthenia.

In many cases the frequency of these events during initiation of therapy may be minimized by careful individualization of starting dosage, slow titration, and the avoidance of large swings in the plasma concentrations of the opioid. Many of these adverse events will cause or decrease in intensity as OxyContin therapy is continued and some degree of tolerance is developed.

Clinical trials comparing OxyContin with immediate-release oxycodone and placebo revealed a similar adverse event profile between OxyContin and immediate-release oxycodone. The most common adverse events (>5%) reported by patients at least once during therapy were:

	OxyContin (n=227)	Immediate-Release (n=225)	Placebo (n=45)
	(%)	(%)	(%)
Constipation	(23)	(26)	(7)
Nausea	(23)	(27)	(11
Somnolence	(23)	(24)	(4)
Dizziness	(13)	(16)	(9)
Pruritus	(13)	(12)	(2)
Vomiting	(12)	(14)	(7)
Headache	(7)	(8)	(7)
Dry Mouth	(6)	(7)	(2)
Asthenia	(6)	(7)	—
Sweating	(5)	(6)	(2)

The following adverse experiences were reported in OxyContin®-treated patients with an incidence between 1% and 5%. In descending order of frequency they were anorexia, nervousness, insomnia, fever, confusion, diarrhea, abdominal pain, dyspepsia, rash, anxiety, euphoria, dyspnea, postural hypotension, chills, twitching, gastritis, abnormal dreams, thought abnormalities, and hiccups.

The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience.

General: accidental injury, chest pain, facial edema, malaise, neck pain, pain

Cardiovascular: migraine, syncope, vasodilation, ST depression

Digestive: dysphagia, eructation, flatulence, gastrointestinal disorder, increased appetite, nausea and vomiting, stomatitis, ileus

Hemic and Lymphatic: lymphadenopathy

Metabolic and Nutritional: dehydration, edema, hyponatremia, peripheral edema, syndrome of inappropriate antidiuretic hormone secretion, thirst

Nervous: abnormal gait, agitation, amnesia, depersonalization, depression, emotional lability, hallucination, hyperkinesia, hypesthesia, hypotonia, malaise, paresthesia, seizures, speech disorder, stupor, tremulus, tremor, vertigo, withdrawal syndrome with or without seizures

Respiratory: cough increased, pharyngitis, voice alteration

Skin: dry skin, exfoliative dermatitis, urticaria

Special Senses: abnormal vision, taste perversion

Urogenital: amenorrhea, decreased libido, dysuria, hematuria, impotence, polyuria, urinary retention, urination impaired

OVERDOSAGE

Acute overdosage with oxycodone can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, bradycardia, hypotension, and death.

Deaths due to overdose have been reported with abuse and misuse of OxyContin®, by ingesting, inhaling, or injecting the crushed tablets. Review of case reports has indicated that the risk of fatal overdose is further increased when OxyContin is abused concurrently with alcohol or other CNS depressants, including other opioids.

In the treatment of oxycodone overdose, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. Supportive measures (including oxygen and vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

The pure opioid antagonists such as naloxone or nalmefene are specific antidotes against respiratory depression from opioid overdose. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to oxycodone overdose. In patients who are physically dependent on any opioid agonist including OxyContin®, an abrupt or complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Please see the prescribing information for the specific opioid antagonist for details of their proper use.

Managing Expected Opioid Adverse Experiences

Most patients receiving opioids, especially those who are opioid-naive, will experience side effects. Frequently the side effects from OxyContin are transient, but may require evaluation and management. Adverse events such as constipation should be anticipated and treated aggressively and prophylactically with a stimulant laxative and/or stool softener. Patients do not usually become tolerant to the constipating effects of opioids.

Other opioid-related side effects such as sedation and nausea are usually self-limited and often do not persist beyond the first few days. If nausea persists and is unacceptable to the patient, treatment with antiemetics or other modalities may relieve these symptoms and should be considered.

Patients receiving OxyContin® may pass an intact matrix "ghost" in the stool or via colostomy. These ghosts contain little or no residual oxycodone and are of no clinical consequence.

SAFETY AND HANDLING

OxyContin Tablets are solid dosage forms that contain oxycodone which is a controlled substance. Furthermore, oxycodone is controlled under Schedule II of the Controlled Substances Act.

OxyContin has been targeted for theft and diversion by criminals. Healthcare professionals should contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

Store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

Healthcare professionals can telephone Purdue Pharma's Medical Services Department (1-888-726-7535) for information on this product.

CAUTION

DEA Order Form Required.

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U.S. Patent Numbers 4,861,598; 4,970,075; 5,266,331; 5,508,042; 5,549,912; and 5,656,295

July 18, 2001

Continue colonoscopy screening in stable patients, regardless of age

Source: American College of Gastroenterology 66th Annual Scientific Meeting, Las Vegas, October 19-24, 2001

In deciding when to stop using colonoscopy to screen older patients for colorectal cancer, physicians should focus on the patient's medical status, not age, according to researchers from the Cleveland Clinic Foundation.

"There are many national guidelines that recommend colon cancer screening with colonoscopy. All of them give an age at which doctors should begin screening, but none say when to stop," said study co-author Carol Burke, MD. "[We found] there isn't an age at which the risk of neoplasia drops significantly so that we would stop screening," she told Geriatrics.

Dr. Burke and colleague Tyler Stevens collected data from records of all colonoscopies performed at the Cleveland Clinic Foundation between 1997 and 2000. They selected colonoscopies performed for colorectal cancer screening in asymptomatic patients or in symptomatic patients with abdominal pain or a change in bowel habits. Because current recommendations are based on patients' risk of developing colonic neoplasias, the researchers analyzed the effect of age and gender on the prevalence of neoplasia, including ≥3 adenomatous polyps, or advanced polyps—defined as tubulovillous, villous, with severe dysplasia, or size ≥1 cm.

Researchers included 981 colonoscopy patients in their analysis:

- 359 age 50 to 60
- 271 age 61 to 70
- 298 age 71 to 80
- 53 age 81 to 100.

Of the examinations, 52% were performed for screening and 48% for symptoms. Prevalence of all neoplasias was:

- 17% in the 50 to 60 age group
- 25% in the 61 to 70 group
- 20% in the 71 to 80 group
- 15% in the 81 to 100 group.

Prevalence of advanced polyps was 3, 2, 5, and 7.5% in the four respective groups. Prevalence of ≥3 adenomatous polyps was 3, 1.5, 3.5, and 4.7% in the four respective groups. Colorectal cancer was detected in four subjects: one in the 50 to 60 age group, one in the 71 to 80 age group, and two in the 81 to 100 age group. The latter three were symptomatic.

Researchers found a marginal association between age and prevalence of neoplasia (p=0.053) that was most significant for the two younger age groups (p=0.010). Increasing age was associated with colorectal cancer (p=0.016) but not with ≥3 polyps (p=0.53)or with advanced polyps (p=0.51).

The prevalence of neoplasia peaked in the seventh decade and declined thereafter, although not significantly. An age-related increase in colorectal cancer was seen after the seventh decade, and all cancers in those age >60 were symptomatic.

For those who were asymptomatic at screening, incidence of neoplasia was 25%, incidence of advanced polyps was 6%, incidence of ≥3 adenomatous polyps was 11% and incidence of invasive cancers was 0.5%.

"No matter what the indication for the exam, there is no difference in the percentage of patients who will have neoplasia," said Dr. Burke, director, Center for Colon Cancer and Polyps, department of gastroenterology, Cleveland Clinic Foundation. "Don't let an elderly person who's due for an exam not get it because he is not having symptoms," she said.

The decision to discontinue screening should be based on the health status of the patient, including whether or not he or she is too frail to undergo preparation for the exam, withstand a complication from colonoscopy, or survive surgery if cancer is detected, Dr. Burke said.

FDA Approval

Rheumatoid arthritis—The interleukin-1 receptor antagonist anakinra (Kineret) was approved for the reduction of signs and symptoms of moderate to severe rheumatoid arthritis (RA) in adult patients who have failed one or more disease-modifying antirheumatic drugs (DMARDs). It can be used alone or in combination with DMARDs other than tumor necrosis factor (TNF) blocking agents. The efficacy of anakinra was evaluated in three randomized, double-blind, placebo-controlled trials that included 1,392 patients age 18 and older. In two studies, patients were on a stable dose of methotrexate and in addition received anakinra or placebo; in the third study, patients received anakinra or placebo alone. In all three studies, the improvement in signs and symptoms of RA was greater among patients taking anakinra than those taking placebo. Recommended dose is 100 mg/d administered by SC injection. The most serious adverse reactions included serious infections such as cellulitis, pneumonia, and bone and joint infections; and neutropenia, particularly when used in combination with TNF-blocking agents.

Risk of death is increased for older patients who gradually lose weight

Source: Journal of the American Geriatrics Society, October 2001

Even a gradual decline in weight can increase older patients' risk of death, according to an analysis of data from the Cardiovascular Health Study (CHS). Weight loss of 5% over a 3-year period is associated with factors that reflect poor health, researchers said.

Physicians have been trained to identify patients who exhibit signifi-

cant weight loss and evaluate them for intestinal disorders, cancer, or other health problems, said principle investigator Anne B. Newman, MD. "What made this study different is we looked at a fairly small decline in weight that physicians probably wouldn't notice unless they were specifically looking for it," she said.

In addition to evaluating whether changes in weight of at least 5% predicted mortality, researchers sought to identify health and behavioral factors that were associated with weight change. They included 4,255 participants age 65 and older who had weight measurements taken during the first and third annual examinations of the CHS. They excluded subjects who were living in an institution, were wheelchair-bound at home, or were receiving treatment for cancer. Weight change was defined as:

- stable if 3-year weight was within ±5% of baseline weight
- loss if weight decreased ≥5% from baseline and
- gain if weight increased ≥5% from baseline.

Dieting behavior, health status, and physical and cognitive function were assessed. Body mass index, body mass distribution, physical activity, smoking status, and alcohol use also were determined.

Researchers found that subjects who lost at least 5% of weight were at increased risk of death, regardless of baseline weight and whether or not they were dieting. Those who lost weight were more than twice as likely to die before the end of follow-up than those whose weight remained stable.

Unlike the approach to patients who lose large amounts of weight and require a thorough work-up to rule out serious illness, the approach to those who gradually lose weight should focus on risk factors such as poor appetite, difficulty obtaining food, oral health problems, and constipation, said Dr. Newman, associate professor of medicine and epidemiology, University of Pittsburgh School of Medicine. Baseline and interim risk factors associated with weight loss included older age, black race, high baseline weight, low waist circumference, smoking, history of stroke, taking multiple medications, hospitalization during the study period, death of a spouse during the study period, high disability in activities of daily living, slow gait speed, and low grip strength.

"I think many doctors are only addressing big weight losses," Dr. Newman said. "What we hope this research points to is the need to pay attention to gradual weight loss and all of the factors that can contribute to it in older people."

SSRIs may cause GI bleeding in certain patients

Source: British Medical Journal, September 22, 2001

Selective serotonin reuptake inhibitor (SSRI) antidepressants may increase risk of GI bleeding for two specific groups of patients, according to researchers from Canada.

"For patients with previous GI bleeding and for those age 80 and older, upper GI bleeding is another factor physicians can consider when weighing the pros and cons of the classes of antidepressants," said study co-author Carl van Walraven, MD.

Although previous studies have indicated an association between bleeding events and SSRIs, they have not specifically classified the antidepressants by the extent to which they inhibit serotonin reuptake and how this inhibition is associated with GI bleeding. To determine the association between GI bleeding and inhibition of serotonin reuptake by antidepressants, researchers analyzed data from a medical database for 317, 824 Ontario residents (age 65 and older) for a 6-year period. Patients were receiving antidepressant therapy and were followed until they stopped taking the drug, were hospitalized with upper GI bleeding, died, or the study ended.

Antidepressants were grouped into low, intermediate, or high categories, based on how much the drug inhibits serotonin reuptake. The "high" category consisted of three SSRIs and one tricyclic antidepressant. The "intermediate" category consisted of one SSRI, two tricyclics, and one other antidepressant. The "low" category consisted of six tricyclics, one tetracyclic antidepressant, and three other antidepressants. During 132,812 person-years of follow-up, there were 974 admissions to the hospital for upper GI bleeding.

Inhibition of serotonin reuptake slightly increased the risk of upper GI bleeding, with a risk of 6.6 GI bleeds per 1,000 person-years for antidepressants in the low inhibition category and a risk of 7.9 bleeds per 1,000 person-years in the high category.

After controlling for age, the risk of upper GI bleeding increased by 10.7% for each higher inhibition group. For octogenarians, risk of bleeding increased from 10.6 per 1,000 person-years in the low inhibition group to 14.7 per 1,000 person-years in the high group.

After controlling for previous upper GI bleeding, the risk of bleeding increased by 9.8% for each higher inhibition group. For patients with a history of previous GI bleeding, risk increased from 28.6 per 1,000 person-years in the low inhibition group to 40.3 per 1,000 person-years in the high group.

Although increased GI bleeding is clinically important and should be considered for patients in these two risk groups, it is an uncommon side effect and should be examined along with other information, said Dr. van Walraven, assistant professor of medicine, department of medicine, University of Ottawa, and scientist, Ottawa Health Research Institute, Ottawa Hospital.

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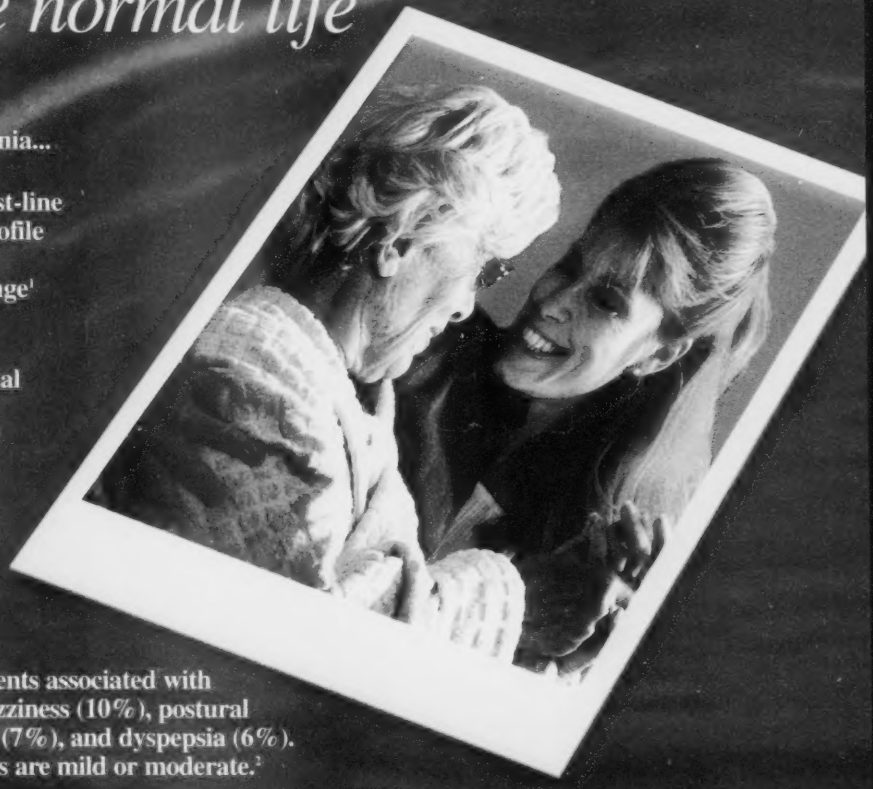

In patients with schizophrenia...

- SEROQUEL is the only first-line treatment with an EPS* profile no different from placebo across the entire dosing range[1]
- Patients treated with SEROQUEL have a minimal need for concomitant anticholinergic medication[2]
- SEROQUEL is proven to reduce both positive and negative symptoms[1-3]

The most common adverse events associated with the use of SEROQUEL are dizziness (10%), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%). The majority of adverse events are mild or moderate.[2]

Consideration should be given to a lower starting dose, a slower rate of dose titration, careful monitoring during the initial dosing period, and a lower target dose in the elderly and patients with hepatic impairment.[2]

As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia, seizures, and orthostatic hypotension.[2]

*Extrapyramidal symptoms.

References: 1. Arvanitis LA, Miller BG, and the Seroquel Trial 13 Study Group. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. *Biol Psychiatry.* 1997;42:233-246. **2.** SEROQUEL® (quetiapine fumarate) Professional Information Brochure, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware. **3.** Small JG, Hirsch SR, Arvanitis LA, et al, and the Seroquel Study Group. Quetiapine in patients with schizophrenia: a high- and low-dose double-blind comparison with placebo. *Arch Gen Psychiatry.* 1997;54:549-557.

Seroquel®
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Please see Brief Summary of full Prescribing Information on following page.

www.SEROQUEL.com

BRIEF SUMMARY of PRESCRIBING INFORMATION

INDICATIONS AND USAGE

SEROQUEL is indicated for the treatment of schizophrenia.

The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Neuroleptic Malignant Syndrome: (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. Two possible cases of NMS [2/2387 (0.1%)] have been reported in clinical trials with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reinitroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported. **Tardive Dyskinesia:** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

PRECAUTIONS: General

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (12/2387) of patients treated with SEROQUEL compared with 0% (0/206) on placebo and about 0.5% (2-4/20) on active control drugs. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid. If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). **Cataracts: The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment. A causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.** **Seizures:** During clinical trials, seizures occurred in 0.8% (18/2387) of patients treated with SEROQUEL compared to 0.5% (1/206) on placebo and 1% (4/420) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older **Hypothyroidism:** Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (10/2386) of SEROQUEL patients did experience TSH increases. Six of the patients with TSH increases needed replacement thyroid treatment. **Cholesterol and Triglyceride Elevations:** In a pool of 3- to 6-week placebo-controlled trials, SEROQUEL-treated patients had increases from baseline in cholesterol and triglyceride of 2.1% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL-treated patients. **Hyperprolactinemia:** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis, Mutagenesis, Impairment of Fertility). Clinical trials and nonclinical studies in rats of experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations (>three times the upper limit of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6%, for SEROQUEL compared to 1% for placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL, especially during the 3-5 day period of initial dose-titration. In the 3- to 6-week placebo-controlled trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Priapism:** One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may have this potential. Severe priapism may require surgical intervention. **Body Temperature Regulation:** Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration. **Dysphagia:** Esophageal dysmotility and aspiration

have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia and close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see Orthostatic Hypotension). **Information for Patients:** Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose. **Interference with Cognitive and Motor Performance:** Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Nursing:** Patients should be advised not to breast feed if they are taking SEROQUEL. **Concomitant Medication:** As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs. **Alcohol:** Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in avoiding overheating and dehydration. **Laboratory Tests:** No specific laboratory tests are recommended. **Drug Interactions:** The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. **The Effect of Other Drugs on SEROQUEL Phenytoin:** Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate). **Thioridazine:** Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg bid). Dosage adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A Inhibitors:** Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin). **Fluoxetine, Imipramine, Haloperidol, and Risperidone:** Administration of fluoxetine (60 mg once daily), imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine. **Effect of Quetiapine on Other Drugs Lorazepam:** The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing. **Lithium:** Concomitant administration of quetiapine (250 mg bid) with lithium (1.5 mEq bid) had no steady-state pharmacokinetic parameters of lithium. **Antipyrine:** Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine. **Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis:** Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There was an increase in pituitary gland adenomas, mammary gland neoplasms, and pancreatic islet cell adenomas in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis). Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat. However, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**). **Mutagenesis:** The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* chromosome damage assay (human lymphocytes) and was negative. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats. **Impairment of Fertility:** Quetiapine had no effect on fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis. **Pregnancy: Pregnancy Category C:** The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis. In rabbits at doses of 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg, and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects on parturition were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of SEROQUEL on labor and delivery in humans is unknown.

SEROQUEL® (quetiapine fumarate) Tablets

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed. **Pediatric Use:** The safety and effectiveness of SEROQUEL in pediatric patients have not been established. **Geriatric Use:** Of the approximately 2400 patients in clinical studies with SEROQUEL, 8% (190) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients.

ADVERSE REACTIONS

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: The most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were dizziness (10^{a}), postural hypotension (7%), dry mouth (7%), and dyspepsia (6%). The following treatment-emergent adverse experiences occurred at an incidence rate of 1% or more, and were at least as frequent among SEROQUEL treated patients, treated at doses of 75 mg/day or greater than among placebo treated patients in 3- to 6-week placebo-controlled trials.[1]

Body as a Whole: Headache. Asthenia. Abdominal pain. Back pain. Fever. **Nervous System:** Somnolence. Dizziness. **Digestive System:** Constipation. Dry Mouth. Dyspepsia. **Cardiovascular System:** Postural hypotension. Tachycardia. **Metabolic and Nutritional Disorders:** Weight gain. **Skin and Appendages:** Rash. **Respiratory System:** Rhinitis. **Special Senses:** Ear pain.

[1]Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but include: accidental injury, infection, chest pain, hostility, accidental injury, hypertension, hypotension, nausea, vomiting, diarrhea, myalgia, agitation, insomnia, anxiety, nervousness, akathisia, hypertonia, tremor, depression, paresthesia, pharyngitis, dry skin, amblyopia and urinary tract infection.

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors. **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials** Dose related **Adverse Events:** Spontaneously elicited adverse event data from a study comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p \leq 0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain. Extrapyramidal Symptoms: Data from one 6-week clinical trial comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. In three additional placebo-controlled clinical trials using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS. **Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**). **Weight Gain:** The proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**). An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo. **ECG Changes:** Between group comparisons for pooled placebo-controlled trials revealed no statistically significant differences between SEROQUEL and placebo patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute with placebo treatment. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**). **Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL:** Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during premarketing testing that is within the premarketing database of approximately 2200 patients. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Nervous System:** *Frequent:* hypertonia, dysarthria; *Infrequent:* abnormal dreams, dyskinesia, thinking abnormal, lurdex dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; *Rare:* aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, paralysis, subdural hematoma. **Body as a Whole:** *Frequent:* flu syndrome; *Infrequent:* neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; *Rare:* abdomen enlarged. **Digestive System:** *Frequent:* anorexia; *Infrequent:* increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, tooth disorder, gastroesophageal reflux, glossitis, hepatic failure, increased rectal hemorrhage, tongue edema; *Rare:* glossitis, hematemesis, intestinal obstruction, melena, pancreatitis. **Cardiovascular System:** *Frequent:* palpitation; *Infrequent:* vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; *Rare:* angina pectoris, atrial fibrillation, AV block, cardiomyopathy, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration. **Respiratory System:** *Frequent:* pharyngitis, rhinitis, cough increased, dyspnea; *Infrequent:* pneumonia, epistaxis, asthma; *Rare:* hiccup, hyperventilation. **Metabolic and Nutritional System:** *Frequent:* peripheral edema; *Infrequent:* weight loss, alkaline phosphatase increased, hyperglycemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hyperglycemia; *Rare:* glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages System:** *Frequent:* sweating; *Infrequent:* pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; *Rare:* exfoliative dermatitis, psoriasis, skin discoloration. **Urogenital System:** *Infrequent:* dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal hemorrhage*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis*, orchitis*. *Rare:* gynecomastia*, nocturia, polyuria, acute kidney failure. **Special Senses:** *Infrequent:* conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; *Rare:* abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System:** *Infrequent:* pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain. **Hemic and Lymphatic System:** *Frequent:* leukopenia; *Infrequent:* leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia, lymphadenopathy, cyanosis; *Rare:* hemolysis, thrombocytopenia. **Endocrine System:** *Infrequent:* hypothyroidism, diabetes mellitus; *Rare:* hyperthyroidism. *adjusted for gender **Post Marketing Experience:** Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include the following: rarely leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Rev 1/01

Manufactured for:
AstraZeneca Pharmaceuticals LP
Wilmington, Delaware 19850-5437

Derm DDx

Flat, pearl-colored plaque

Consider various carcinomas in a patient with a history of skin cancers

Norman Levine, MD

Figure. Solitary eroded plaque on the trunk.

For several years, a 78-year-old man has had a slowly enlarging, asymptomatic spot on his back. He has a history of skin cancers and actinic keratoses on the face and hands.

On examination, you observe a solitary, 2 cm, smooth, shiny, pearl-colored plaque with punctate erosions. The lesion is almost flat and is not substantive. There is no surrounding inflammation (figure).

Differential diagnosis

Skin conditions to consider are those that cause superficial plaques on the trunk.

Seborrheic keratosis may be solitary, is superficial, and may have a pearly color if it becomes inflamed. The erosion on the surface of this patient's lesion and the absence of roughness or scale makes this diagnosis unlikely.

Squamous cell carcinoma (SCC) is common in patients with previous skin cancers and may appear on the trunk as an eroded plaque. SCC lesions are usually indurated or otherwise substantive, however, and often have surrounding erythema.

Bowen's disease (carcinoma-in-situ) presents as a solitary, nonsubstantive reddish plaque that can be difficult to distinguish from the lesion seen here. Overlying scale and thinning of the epidermis are subtle clues that help make this diagnosis. Biopsy is often needed to confirm this skin condition.

Superficial basal cell carcinoma is the correct diagnosis. It occurs on the trunk and extremities and is a common form of basal cell carcinoma. It differs from nodular or sclerosing basal cell carcinomas of the head and neck because it does not deeply invade the skin, may erode but does not ulcerate, and never metastasizes.

The lesion resolved completely with destruction by electrodesiccation and curettage.

Diagnostic pearl

Superficial basal cell carcinoma occurs as a slow-growing nonsubstantive pearly papule on the trunk.

Dr. Levine is chief of dermatology, University of Arizona Health Sciences Center, Tucson.

Infectious disease

Influenza

How to prevent and control nursing home outbreaks

Irving H. Gomolin, MD • Rakesh K. Kathpalia, MD

Influenza is an important cause of acute respiratory illness among older adults in general and within the nursing home in particular. Epidemics typically are reported in the late fall and throughout the winter. In the nursing home, vaccination may not prevent clinical illness but can reduce the risk of pneumonia, hospitalization, and death. Atypical presentations, including delirium and nonspecific functional changes, are common in older patients. Rapid diagnosis is imperative, as early antiviral treatment and prophylaxis can control a nursing home outbreak.

Gomolin IH, Kathpalia RK. Influenza: How to prevent and control nursing home outbreaks. Geriatrics 2002; 57(Jan):28-34.

Influenza is an important cause of acute respiratory illness among older adults in general and within the nursing home in particular. Physicians managing an influenza outbreak in the nursing home face special clinical challenges:

- Although typically considered an acute self-limiting illness, influenza poses an increased risk of serious complications—including death—for the frail older patient with underlying chronic disease.
- Crowding elevates the risk of infection in the nursing home, as does exposure from staff and visitors who live in the community.

Sporadic influenza infection occurs year round, but epidemics typically are reported in the late fall and throughout the winter. This article describes the clinical features of influenza and its atypical presentations in older patients, the use of rapid diagnostic techniques, the utility of late-season vaccinations, and a treatment and prophylaxis strategy to manage suspected influenza outbreaks in the nursing home.

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Influenza virus

Three types of influenza virus—A, B, and C—are recognized. Type C disease is uncommon, and type B illness is typically less severe than type A. Influenza A subtypes depend on the antigenic properties of surface glycoproteins contained in the lipid envelope of the virus. Influenza B viruses are not categorized into subtypes.[1]

Influenza viruses have a lipid envelope that contains immunogenic hemagglutinin (H) and neuraminidase (N) glycoproteins. Hemagglutinin helps the virus bind to cell receptors, and neuraminidase degrades the receptors and facilitates release of virus into the cell. Major immunity against influenza is associated with development of antibodies against the H antigen. Antibodies against the N antigen decrease the release of virus and help limit the infection.[2]

The H and N antigens undergo periodic variation, resulting in epidemics among populations that have little or no resistance to a changed virus. Antigenic variation may be minor (antigenic drift) or major (antigenic shift).[1,2] The 2001-2002 trivalent vaccine virus strains are A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Sichuan/379/99-like.[3]

Clinical features

In the community, epidemics tend to begin abruptly, reach a peak in 2 to 3 weeks, and last about 5 to 10 weeks.[4] Diagnosis is suspected from clinical features and confirmed with laboratory testing. Transmission typically occurs after contact with the aerosolized respiratory secretions of an acutely infected person. Viral shedding begins at the onset of symptoms and continues for 3 to 5 days.

Presentation. Clinical presentation and severity of illness vary widely. In the classic presentation, onset is sudden. Systemic symptoms such as fever, chills, myalgia, headache, and malaise predominate for the first 3 to 4 days. Rhinitis or pharyngitis may also occur. As systemic symptoms subside, respiratory symptoms such as sore throat,

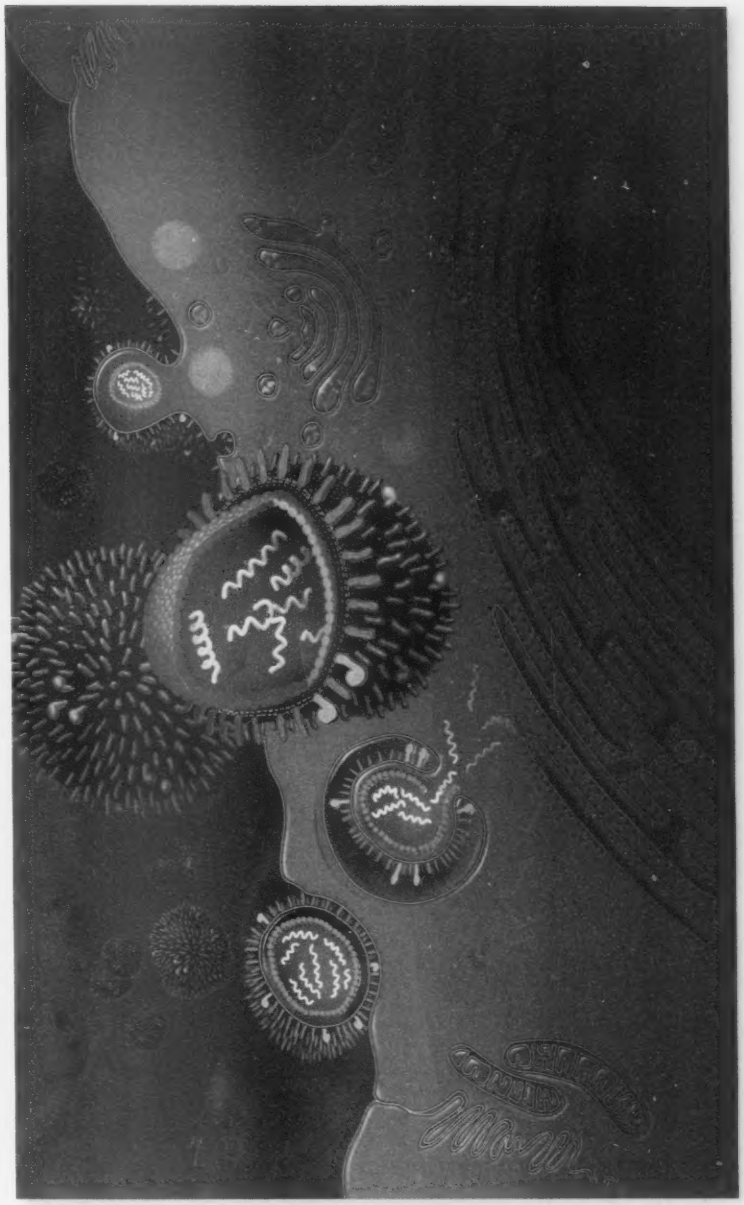
dry cough, rhinorrhea, and wheezing tend to become the major complaint and typically last for a few days, unless pneumonia supervenes.[1,5]

Atypical presentations are common in older patients. Especially in the nursing home, nonspecific symptoms such as fever with lethargy or delirium and changes in functional status are seen more often than the classic presentation. Patients with dementia and/or aphasias cannot report myalgia, sore throat, or malaise.

Thus, the clinician must maintain a high index of suspicion and consider the diagnosis of influenza when clusters of residents develop fever, systemic signs, and respiratory complaints during the influenza season. A case of influenza-like illness (ILI) is defined as the presence of respiratory symptom(s) and a fever of ≥100 °F.[6,7]

Differential diagnosis. Other viral illnesses including respiratory syncytial virus, parainfluenza, and adenovirus can cause similar institutional outbreaks. Laboratory confirmation is therefore imperative in the nursing home because antiviral agents can effectively treat influenza illness and suppress an epidemic. When compared with viral cultures, reported sensitivity and specificity of clinical definitions for ILI are 63 to 78% and 55 to 71%, respectively, although these rates may vary depending on influenza and other viral activity in the community.[8,9]

Complications. Uncomplicated influenza generally resolves spontaneously within a week. In frail older patients, however, postinfluenza asthenia may persist for weeks.[1] Major complications are primary viral pneumonia, secondary bacterial pneumonia (often with *Streptococcus pneumoniae, Staphylococcus aureus,* or *Hemophilus influenzae*), exacerbation of chronic lung and heart disease, and death. Cognitively-impaired nursing home residents are at particular risk for dehydration due to increased insensible water loss due to fever and tachypnea, worsened by decreased oral intake. They are also prone to skin breakdown due to immobility and to fecal impaction due to immobility and dehydration.



Influenza virions, sectioned to show the capsid and RNA. This drawing depicts the entry of the virus into a cell (bottom), where the introduced RNA causes the cell's golgi apparatus to produce new viral proteins. These proteins are transported to the cell surface and become part of the resynthesized viral capsid, filled with viral RNA (top).

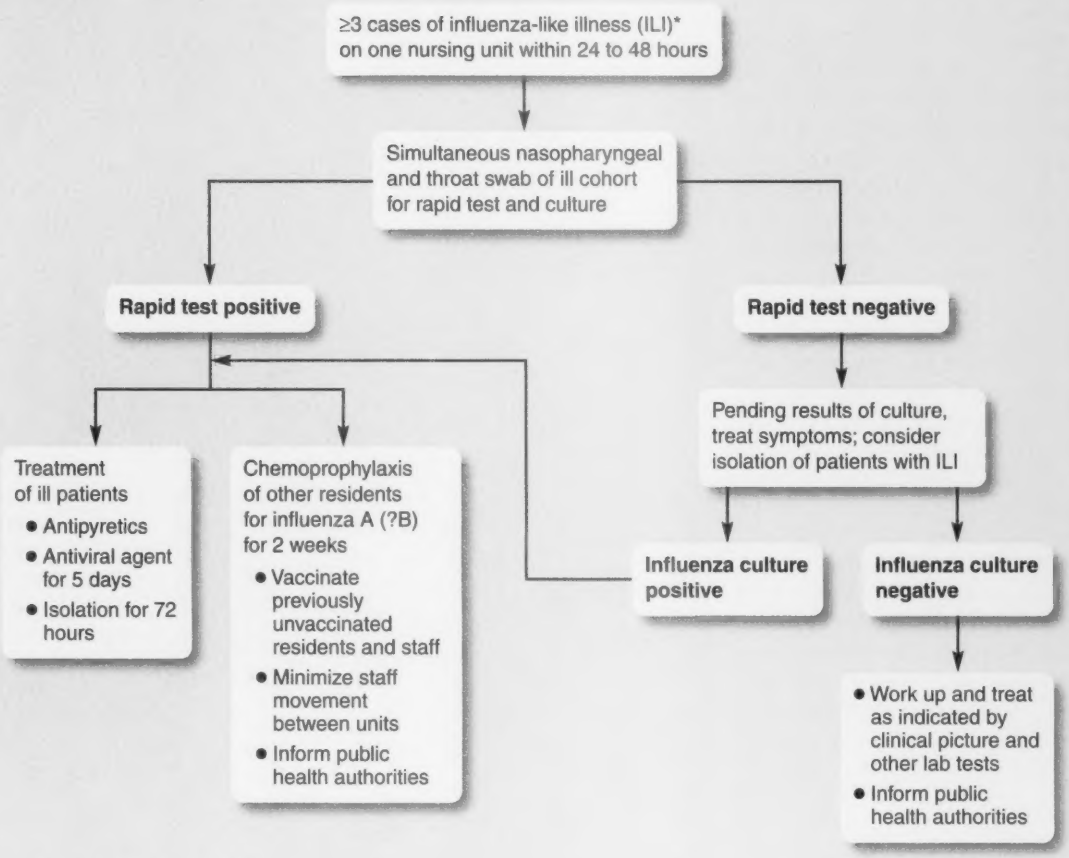
Illustration for Geriatrics by David Baker

Diagnosis

Rapid diagnosis is imperative at the start of an outbreak in a nursing home (figure). An influenza A epidemic can be contained by initiating treatment and isolation of affected individuals within 24 to 48 hours and providing chemoprophylaxis to other residents. Little or no information is available on the use of antiviral therapy during influenza B outbreaks in nursing homes.[8]

continued

Figure Management of a suspected influenza outbreak in the nursing home


≥3 cases of influenza-like illness (ILI)* on one nursing unit within 24 to 48 hours
Simultaneous nasopharyngeal and throat swab of ill cohort for rapid test and culture
Rapid test positive
Rapid test negative
Treatment of ill patients
• Antipyretics
• Antiviral agent for 5 days
• Isolation for 72 hours
Chemoprophylaxis of other residents for influenza A (?B) for 2 weeks
• Vaccinate previously unvaccinated residents and staff
• Minimize staff movement between units
• Inform public health authorities
Pending results of culture, treat symptoms; consider isolation of patients with ILI
Influenza culture positive
Influenza culture negative
• Work up and treat as indicated by clinical picture and other lab tests
• Inform public health authorities

* Influenza-like illness (ILI) is defined as respiratory symptoms and temperature ≥100 °F

Source: Prepared for Geriatrics by Irving H. Gomolin, MD, and Rakesh K. Kathpalia, MD

Rapid assay. Assay kits are available for rapid testing of nasopharyngeal and/or throat swab specimens for the presence of A or B viruses. Positive results depend on viral quantity, which is greatest at the onset of illness. Therefore, samples should be taken from clusters of recently ill residents to allow early intervention and to increase the likelihood of identifying an outbreak. An outbreak is defined as a cluster of three or more cases of ILI on a single nursing unit within 24 to 48 hours.[6]

Culture. Specimens obtained for rapid testing are also submitted for viral culture to acquire definitive information on the circulating viral strain and subtype. Culture is helpful in assessing vaccine efficacy for the current season and provides guidance for vaccine formulation for the next season. Prior to each influenza season, nursing home staff should purchase culture supplies and make arrangements to transport specimens and obtain laboratory testing, including prompt notification of rapid test results.

Prevention

Vaccination is the most effective method to reduce the risk of influenza. The Centers for Disease Control and Prevention (CDC) recommends vaccination during the 2001-2002 influenza season for high-risk persons, including:

- those age 65 and older
- residents of nursing homes and other chronic-care facilities
- persons of any age with chronic disorders of the pulmonary and cardiovascular systems, including asthma
- persons who require regular follow-up or hospitalization for chronic metabolic disorders, including diabetes, renal dysfunction, hemoglobinopathies, or immunosuppression.

Healthy persons age 50 to 64, nursing home staff and others who come in contact with high-risk individuals, and persons who want to reduce their

Nighttime heartburn: a rude awakening

PROTONIX® tames erosive GERD night after night

PROTONIX is indicated for the treatment and maintenance of healing of erosive esophagitis with associated gastroesophageal reflux disease (GERD) symptoms. Controlled studies did not extend beyond 12 months.

The most frequently reported adverse events with PROTONIX Delayed-Release Tablets are headache and diarrhea. Symptomatic response to therapy does not preclude the presence of gastric malignancy. PROTONIX is contraindicated in patients with known hypersensitivity to any component of the formulation. **Please see brief summary of Prescribing Information on adjacent page.**

ONCE-A-DAY

PROTONIX® 40mg

(Pantoprazole Sodium) Delayed-Release Tablets

Makes erosive GERD nights *good* nights™

PROTONIX® 40mg

(Pantoprazole Sodium) Delayed Release Tablets

Makes erosive GERD nights good nights™

See package insert for full Prescribing Information.

INDICATIONS AND USAGE

Maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with gastroesophageal reflux disease (GERD). Controlled studies did not extend beyond 12 months.

Short-term treatment (up to 8 weeks) of erosive esophagitis associated with GERD. For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered.

CONTRAINDICATIONS

Known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

Owing to the chronic nature of erosive esophagitis, there may be a potential for prolonged administration of pantoprazole. In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown.

Information for Patients

PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach and should not be split, crushed, or chewed. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when coadministered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis, of a 50 kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of combined hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

A 26-week p53 +/- transgenic mouse carcinogenicity study was not positive.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* ASS2/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

Erosive esophagitis healing rates in the 221 women treated with PROTONIX (pantoprazole sodium) Delayed-Release Tablets in U.S. clinical trials were similar to those found in men. In the 122 women treated long term with PROTONIX 40 mg or 20 mg, healing was maintained at a rate similar to that in men. The incidence rates of adverse events were also similar for men and women.

Use in Elderly

In short-term U.S. clinical trials, erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with PROTONIX were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

ADVERSE REACTIONS

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with PROTONIX.

Most Frequent Adverse Events Reported as Drug Related in Short-term Domestic Trials

	% Incidence			
	Study 300-US		Study 301-US	
Study Event	PROTONIX (n = 521)	Placebo (n = 82)	PROTONIX (n = 161)	Nizatidine (n = 82)
Headache	6	6	9	13
Diarrhea	4	1	6	6
Flatulence	2	2	4	0
Abdominal pain	1	2	4	4
Rash	<1	0	2	0
Eructation	1	1	0	0
Insomnia	<1	2	1	1
Hyperglycemia	1	0	<1	0

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In international short-term double-blind or open-label clinical trials involving 20 to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Adverse Events in GERD Patients in Short-term International Trials

	% Incidence			
Study Event	Pantoprazole Total (N = 2805)	Ranitidine 300 mg (N = 594)	Omeprazole 20 mg (N = 474)	Famotidine 40 mg (N = 239)
Headache	2	3	2	1
Diarrhea	2	2	2	<1
Abdominal Pain	1	1	<1	<1

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 12 months, the following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more of GERD patients on long-term therapy.

Most Frequent Adverse Events Reported as Drug Related in Long-term Domestic Trials

	% Incidence	
Study Event	PROTONIX (n = 536)	Ranitidine (n = 185)
Headache	5	2
Abdominal pain	3	1
Liver function tests abnormal	2	<1
Nausea	2	2
Vomiting	2	2

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short- and long-term domestic and international trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥1% in pantoprazole-treated patients: anxiety, arthralgia, asthenia, back pain, bronchitis, chest pain, constipation, cough increased, dizziness, dyspepsia, dyspnea, flu syndrome, gastroenteritis, gastrointestinal disorder, hyperlipemia, hypertonia, infection, liver function tests abnormal, migraine, nausea, neck pain, pain, pharyngitis, rectal disorder, rhinitis, SGPT increased, sinusitis, upper respiratory tract infection, urinary frequency, urinary tract infection, and vomiting.

Additional treatment-emergent adverse experiences occurring in <1% of pantoprazole-treated patients from these trials are listed below by body system. In most instances the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, nonspecified drug reaction, photosensitivity reaction.

CARDIOVASCULAR SYSTEM: abnormal electrocardiogram, angina pectoris, arrhythmia, atrial fibrillation/flutter, cardiovascular disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial infarction, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, neuropathy, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pruritus, skin disorder, skin ulcer, sweating, urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

There have been spontaneous reports of adverse events with the postmarketing use of pantoprazole. These reports include anaphylaxis (including anaphylactic shock), angioedema (Quincke's edema), anterior ischemic optic neuropathy, severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; pancreatitis; and rhabdomyolysis. In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

Laboratory Values

In two U.S. controlled, short-term trials, 0.4 % of the patients on PROTONIX 40 mg experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. In two U.S. controlled, long-term trials, none of 178 patients (0%) on PROTONIX 40 mg and two of 181 patients (1.1%) on PROTONIX 20 mg experienced significant transaminase elevations at 12 months (or earlier if a patient discontinued prematurely). Significant elevations of SGOT or SGPT were defined as values at least three times the upper limit of normal that were non-sporadic and had no clear alternative explanation. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient tolerated a dose of 320 mg per day for 3 months. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

Pantoprazole is not removed by hemodialysis.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

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Byk Gulden Pharmaceuticals
D78467 Konstanz, Germany

This Brief Summary is based on the approved PROTONIX Delayed-Release Tablets direction circular (CI 7482-1, Issued June 18, 2001).

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risk of influenza should also be offered vaccinations for as long as influenza remains active and vaccine is available, according to the CDC.

In the nursing home, vaccination may not prevent clinical illness, but it can reduce the risk of pneumonia, hospitalization, and death.[10] Vaccine side effects include soreness at the injection site and (infrequently) low-grade fever for 24 to 48 hours. Vaccination of all nursing home employees may reduce the likelihood of introduction and transmission of influenza, as well as reduce staff absenteeism due to illness.[11]

Influenza activity generally begins after December and continues until March. Although optimal vaccination time is October through mid-November, vaccine shortages delayed administration in 2000 and 2001. Vaccine should be offered to all nonimmunized, community-living older adults and those newly admitted to nursing homes throughout the influenza season. Prophylactic antiviral therapy during the 2 weeks required for the development of a protective response should be considered for high-risk persons who receive vaccination during an outbreak.

Table Antiviral treatment and prophylaxis of influenza in the nursing home patient*

Agent	Virus types	Administration
Amantadine HCl Symmetrel (capsules, syrup)	A	Treatment or prophylaxis based on serum creatinine: ≤1.0 mg/dL: 100 mg/d >1.0 to ≤2.0: 100 mg every other day >2.0: 100 mg twice per week On dialysis: 100 mg once per week
Rimantadine HCl Flumadine (tablets, syrup)	A	Treatment or prophylaxis: 100 mg/d Consult drug package insert for dosage recommendations for administering to persons with severe hepatic dysfunction or creatinine clearance ≤10 mL/min
Oseltamivir phosphate Tamiflu (capsules, powder for oral suspension)	A and B	Treatment: 75 mg bid Prophylaxis: 75 mg/d Reduction in dosage is recommended for persons with creatinine clearance <30 mL/min
Zanamivir Relenza (5-mg blisters of powder for inhalation)	A and B	Treatment: 10 mg bid (not approved for prophylaxis) Administered via inhalation by using a plastic device included in the package with the medication; may be difficult for nursing home residents to administer

* Administer antiviral agent as treatment for 5 days and as prophylaxis for at least 2 weeks (longer if new cases continue to occur within the nursing home)

Source: Prepared for Geriatrics by Irving H. Gomolin, MD, and Rakesh K. Kathpalia, MD, based on information contained in references 6 and 8.

Treatment and prophylaxis

Treatment of influenza symptoms includes antipyretics and analgesics, such as acetaminophen, 650 mg every 4 to 6 hrs. Comorbid conditions in older patients and polypharmacy complicate treatment and may require adjustment of therapy.

For example, to avoid dehydration, consider withholding a patient's diuretic therapy until fluid intake improves and fever resolves. Similarly, drugs with sedative properties may need to be withheld for patients who are hypoalert and at risk for inadequate fluid intake. Antibiotics have no role unless bacterial infection supervenes.

Antiviral agents. Antiviral agents are indicated for the treatment of acute illness due to influenza and for prophylaxis during institutional outbreaks. Antiviral treatment within 24 to 48 hours of symptom onset can decrease the severity and duration of uncomplicated acute illness.

Four antiviral agents are available for treatment of the acute respiratory illness caused by influenza (table). Amantadine HCl (Symmetrel) and rimantadine HCl (Flumadine) are active against influenza A, and the neuraminidase inhibitors oseltamivir phosphate (Tamiflu) and zanamivir (Relenza) are active against influenza A and B.[12-14] Zanamivir, which is delivered by inhalation, may be difficult for nursing home residents to administer.

Hospitalization. Indications for hospitalization of a nursing home resident with influenza include complications such as primary viral pneumonia, secondary bacterial pneumonia, exacerbation of COPD, and refractory heart failure. Signs and symptoms such as severe tachypnea, hypoxemia, and hypotension also may warrant hospitalization. Each case is considered on an individual basis, depending on the patient's comorbid conditions.

The threshold for hospitalization may vary among facilities, depending on staffing patterns and physician judgment. Hospitals to which patients are transferred must be informed that the diagnosis is influenza, so that appropriate infection control measures can be instituted.

Prophylaxis. The antivirals amantadine, rimantadine, and oseltamivir are

indicated for prophylaxis of influenza. Most published reports on the use of antiviral agents for institutional prophylaxis are based on experience with amantadine and rimantadine for influenza A.[12] Antiviral prophylaxis is recommended for at least 2 weeks during a presumed outbreak.

As soon as an institutional outbreak is identified, local and state infection control authorities should be consulted for guidance in the use of antiviral agents and other influenza control procedures. These include restriction of movement of ill residents, restriction of staff movement between units, and vaccination of previously unvaccinated staff and residents.

Conclusion

Influenza is a serious acute illness for persons at risk for complications, especially frail nursing home residents. An influenza outbreak should be suspected when a cluster of three or more residents in a single nursing unit develop influenza-like illness within 24 to 48 hours. Nursing homes should arrange to have rapid laboratory testing available, particularly from December through March.

Vaccination is the mainstay of prevention, and antiviral agents are available for treatment and prophylaxis. Influenza outbreaks are reportable to local and state health authorities, who can assist with appropriate management in the long-term care facility.

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For depression in older patients*

Celexa
citalopram HBr™

Effective first-line SSRI therapy with a
favorable side-effect profile

1. Incidence of insomnia, anxiety, agitation, nervousness, and fatigue comparable to placebo[1]
2. Low potential for drug interactions[1,2]
3. Not associated with clinically significant weight changes†[1]
4. Effectively treats depression
5. Available in oral solution
   — sugar-free, alcohol-free solution
   (1 teaspoon contains 10 mg)

Available in oral solution

Visit the CELEXA Web site at http://www.celexa.com

The most frequent adverse events reported with CELEXA vs placebo in clinical trials were nausea (21% vs 14%), dry mouth (20% vs 14%), somnolence (18% vs 10%), insomnia (15% vs 14%), increased sweating (11% vs 9%), tremor (8% vs 6%), diarrhea (8% vs 5%), and ejaculation disorder (6% vs 1%).
CELEXA is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs) or in patients with a hypersensitivity to citalopram HBr or any of the ingredients in CELEXA.

20 mg/day is the recommended dose for most elderly patients and patients with hepatic impairment, with titration to 40 mg/day only for nonresponding patients.

*Patients ≥ 60 years old.
†CELEXA therapy was associated with a mean weight increase of only 1.5 kg after 12 months.

For more information about contraindications, warnings, precautions, adverse reactions, and dosage and administration, please see Brief Summary.

References: 1. Data on file, Forest Laboratories, Inc. **2.** Greenblatt DJ, von Moltke LL, Harmatz JS, Shader RI. Drug interactions with newer antidepressants: role of human cytochromes P450. *J Clin Psychiatry.* 1998;59(suppl 15):19-27.

Celexa
citalopram HBr

Brief Summary: For complete details, please see full prescribing information for Celexa.
INDICATIONS AND USAGE Celexa (citalopram HBr) is indicated for the treatment of depression. The efficacy of Celexa in the treatment of depression was established in 4- to 6-week controlled trials of outpatients whose diagnoses corresponded most closely to the DSM-III and DSM-III-R category of major depressive disorder. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt, or suicidal ideation. The antidepressant action of Celexa in hospitalized depressed patients has not been adequately studied. The efficacy of Celexa in maintaining an antidepressant response for up to 24 weeks following 6 to 8 weeks of acute treatment was demonstrated in two placebo-controlled trials. Nevertheless, the physician who elects to use Celexa for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. **CONTRAINDICATIONS** Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see WARNINGS). Celexa is contraindicated in patients with a hypersensitivity to citalopram or any of the inactive ingredients in Celexa. **WARNINGS Potential for Interaction with Monoamine Oxidase Inhibitors In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRI's and MAOI's suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Celexa should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Celexa before starting an MAOI. PRECAUTIONS General** Hyponatremia Several cases of hyponatremia and SIADH (syndrome of inappropriate antidiuretic hormone secretion) have been reported in association with Celexa treatment. All patients with these events have recovered with discontinuation of Celexa and/or medical intervention. Activation of Mania/Hypomania In placebo-controlled trials of Celexa,some of which included patients with bipolar disorder, activation of mania/hypomania was reported in 0.2% of 1063 patients treated with Celexa and in none of the 446 patients treated with placebo. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with other marketed antidepressants. As with all antidepressants, Celexa should be used cautiously in patients with a history of mania. Seizures Although anticonvulsant effects of citalopram have been observed in animal studies, Celexa has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Celexa, seizures occurred in 0.3% of patients treated with Celexa (a rate of one patient per 96 years of exposure) and 0.5% of patients treated with placebo (a rate of one patient per 50 years of exposure). Like other antidepressants, Celexa should be introduced with care in patients with a history of seizure disorder. Suicide The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy. Prescriptions for Celexa should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Interference With Cognitive and Motor Performance In studies in normal volunteers, Celexa in doses of 40 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgement, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Celexa therapy does not affect their ability to engage in such activities. Use in Patients With Concomitant Illness Clinical experience with Celexa in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Celexa in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Celexa has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 1116 patients who received Celexa in clinical trials were evaluated, and the data indicate that Celexa is not associated with the development of clinically significant ECG abnormalities. In subjects with hepatic impairment, citalopram clearance was decreased and plasma concentrations were increased. The use of Celexa in hepatically impaired patients should be approached with caution and a lower maximum dosage is recommended. Because citalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Celexa, however, it should be used with caution in such patients. **Drug Interactions** CNS Drugs – Given the primary CNS effects of citalopram, caution should be used when it is taken in combination with other centrally acting drugs. Alcohol – Although citalopram did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by depressed patients taking Celexa is not recommended. Monoamine Oxidase Inhibitors (MAOIs) – See CONTRAINDICATIONS and WARNINGS. Cimetidine – In subjects who had received 21 days of 40 mg/day Celexa, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. Digoxin – In subjects who had received 21 days of 40 mg/day Celexa, combined administration of Celexa and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. Lithium – Coadministration of Celexa (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of citalopram, caution should be exercised when Celexa and lithium are coadministered. Theophylline – Combined administration of Celexa (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. Sumatriptan – There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of a selective serotonin reuptake inhibitor (SSRI) and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (eg, fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram) is clinically warranted, appropriate observation of the patient is advised. Warfarin – Administration of 40 mg/day Celexa for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. Carbamazepine – Combined administration of Celexa (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of citalopram should be considered if the two drugs are coadministered. Triazolam – Combined administration of Celexa (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. Ketoconazole – Combined administration of Celexa (40 mg) and ketoconazole (200 mg) decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. CYP3A4 and CYP2C19 Inhibitors – *In vitro* studies indicated that CYP3A4 and CYP2C19 are the primary enzymes involved in the metabolism of citalopram. However coadministration of citalopram (40 mg) and ketoconazole (200 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of citalopram. Because citalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease citalopram clearance. Metoprolol – Administration of 40 mg/day Celexa for 22 days resulted in a two-fold increase in the plasma levels of the beta-adrenergic blocker metoprolol. Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Celexa and metoprolol had no clinically significant effects on blood pressure or heart rate. Imipramine and Other Tricyclic Antidepressants (TCAs) – *In vitro* studies suggest that citalopram is a relatively weak inhibitor of CYP2D6. Coadministration of Celexa (40 mg/day for 10 days) with the tricyclic antidepressant imipramine (single dose of 100 mg), a substrate for CYP2D6, did not significantly affect the plasma concentrations of imipramine or citalopram. However, the concentration of the imipramine metabolite desipramine was increased by approximately 50%. The

clinical significance of the desipramine change is unknown. Nevertheless, caution is indicated in the coadministration of TCAs with Celexa. Electroconvulsive Therapy (ECT) – There are no clinical studies of the combined use of electroconvulsive therapy (ECT) and Celexa. **Pregnancy** Pregnancy Category C – There are no adequate and well-controlled studies in pregnant women; therefore, citalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery** The effect of Celexa on labor and delivery in humans is unknown. **Nursing Mothers** As has been found to occur with many other drugs, citalopram is excreted in human breast milk. The decision whether to continue or discontinue either nursing or Celexa therapy should take into account the risks of citalopram exposure for the infant and the benefits of Celexa treatment for the mother. **Pediatric Use** Safety and effectiveness in pediatric patients have not been established. **Geriatric Use** Of 4422 patients in clinical studies of Celexa,1357 were 60 and over. 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Most elderly patients treated with Celexa in clinical trials received daily doses between 20 and 40 mg. In two pharmacokinetic studies, citalopram AUC was increased by 23% and 30%, respectively, in elderly subjects as compared to younger subjects, and its half-life was increased by 30% and 50%, respectively. 20 mg/day is the recommended dose for most elderly patients. **ADVERSE REACTIONS** The premarketing development program for Celexa included citalopram exposures in patients and/or normal subjects from 3 different groups of studies: 429 normal subjects in clinical pharmacology/pharmacokinetic studies; 4422 exposures from patients in controlled and uncontrolled clinical trials, corresponding to approximately 1370 patient exposure years. There were, in addition, over 19,000 exposures from mostly open-label, European postmarketing studies. The conditions and duration of treatment with Celexa varied greatly and included (in overlapping categories) open-label and double-blind studies, inpatient and outpatient studies, fixed-dose and dose-titration studies, and short-term and long-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Findings Observed in Short-term, Placebo-Controlled Trials** Adverse Events Associated With Discontinuation of Treatment Among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration, 16% discontinued treatment due to an adverse event, as compared to 8% of 446 patients receiving placebo. The adverse events associated with discontinuation and considered drug-related (ie, associated with discontinuation in at least 1% of Celexa-treated patients and at a rate at least twice that of placebo) are shown in **TABLE 1**. It should be noted that one patient can report more than one reason for discontinuation and be counted more than once in this table.

TABLE 1.
Adverse Events Associated With Discontinuation of Treatment in Short-term, Placebo-Controlled Depression Trials

	Percentage of Patients Discontinuing Due to Adverse Event	
Body System/Adverse Event	**Celexa (N=1063)**	**Placebo (N=446)**
General		
Asthenia	1%	<1%
Gastrointestinal Disorders		
Nausea	4%	0%
Dry Mouth	1%	<1%
Vomiting	1%	0%
Central and Peripheral Nervous System Disorders		
Dizziness	2%	<1%
Psychiatric Disorders		
Insomnia	3%	1%
Somnolence	2%	1%
Agitation	1%	<1%

Adverse Events Occurring at an Incidence of 2% or More Among Celexa-Treated Patients **TABLE 2** enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 1063 depressed patients who received Celexa at doses ranging from 10 to 80 mg/day in placebo-controlled trials of up to 6 weeks in duration. Events included are those occurring in 2% or more of patients treated with Celexa and for which the incidence in patients treated with Celexa was greater than the incidence in placebo-treated patients. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence rate in the population studied. The only commonly observed adverse event that occurred in Celexa patients with an incidence of 5% or greater and at least twice the incidence in placebo patients was ejaculation disorder (primarily ejaculatory delay) in male patients (see **TABLE 2**).

TABLE 2.
Treatment-Emergent Adverse Events:
Incidence in Placebo-Controlled Clinical Trials*

	Percentage of Patients Reporting Event	
Body System/Adverse Event	**Celexa (N=1063)**	**Placebo (N=446)**
Autonomic Nervous System Disorders		
Dry Mouth	20%	14%
Sweating Increased	11%	9%
Central & Peripheral Nervous System Disorders		
Tremor	8%	6%
Gastrointestinal Disorders		
Nausea	21%	14%
Diarrhea	8%	5%
Dyspepsia	5%	4%
Vomiting	4%	3%
Abdominal Pain	3%	2%
General		
Fatigue	5%	3%
Fever	2%	<1%
Musculoskeletal System Disorders		
Arthralgia	2%	1%
Myalgia	2%	1%
Psychiatric Disorders		
Somnolence	18%	10%
Insomnia	15%	14%
Anxiety	4%	3%
Anorexia	4%	2%
Agitation	3%	1%
Dysmenorrhea	3%	2%
Libido Decreased	2%	<1%
Yawning	2%	<1%
Respiratory System Disorders		
Upper Respiratory Tract Infection	5%	4%
Rhinitis	5%	3%
Sinusitis	3%	<1%
Urogenital		
Ejaculation Disorder	6%	1%
Impotence	3%	<1%

* Events reported by at least 2% of patients treated with Celexa are reported, except for the following events which had an incidence in placebo :≥Celexa: headache, asthenia, dizziness,

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constipation, palpitation, vision abnormal, sleep disorder, nervousness, pharyngitis, micturition disorder, back pain. Denominator used was for females only (N=638 Celexa; N=252 placebo). Primarily ejaculatory delay. Denominator used was for males only (N=425 Celexa; N=194 placebo). Dose Dependency of Adverse Events The potential relationship between the dose of Celexa administered and the incidence of adverse events was examined in a fixed-dose study in depressed patients receiving placebo or Celexa 10, 20, 40, and 60 mg. Jonckheere's trend test revealed a positive dose response ($p< .05$) for the following adverse events: fatigue, impotence, insomnia, sweating increased, somnolence, and yawning. Male and Female Sexual Dysfunction With SSRI's Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that selective serotonin re-uptake inhibitors (SSRIs) can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence. The table below displays the incidence of sexual side effects reported by at least 2% of patients taking Celexa in a pool of placebo-controlled clinical trials in patients with depression.

Treatment	Celexa (425 males)	Placebo (194 males)
Abnormal Ejaculation (mostly ejaculatory delay)	6.1% (males only)	1% (males only)
Decreased Libido	3.8% (males only)	<1% (males only)
Impotence	2.8% (males only)	<1% (males only)

In female depressed patients receiving Celexa, the reported incidence of decreased libido and anorgasmia was 1.3% (n=638 females) and 1.1% (n=252 females), respectively. There are no adequately designed studies examining sexual dysfunction with citalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRI's, physicians should routinely inquire about such possible side effects. Vital Sign Changes Celexa and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Celexa treatment. In addition, a comparison of supine and standing vital sign measures for Celexa and placebo treatments indicated that Celexa treatment is not associated with orthostatic changes. Weight Changes Patients treated with Celexa in controlled trials experienced a weight loss of about 0.5 kg compared to no change for placebo patients. Laboratory Changes Celexa and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Celexa treatment. ECG Changes Electrocardiograms from Celexa (N=802) and placebo (N=241) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. The only statistically significant drug-placebo difference observed was a decrease in heart rate for Celexa of 1.7 bpm compared to no change in heart rate for placebo. There were no observed differences in QT or other ECG intervals. **Other Events Observed During the Premarketing Evaluation of Celexa** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by patients treated with Celexa at multiple doses in a range of 10 to 80 mg/day during any phase of a trial within the premarketing database of 4422 patients. All reported events are included except those already listed in **TABLE 2** or elsewhere in labeling, those events for which a drug cause was remote, those event terms which were so general as to be uninformative, and those occurring in only one patient. It is important to emphasize that although the events reported occurred during treatment with Celexa, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Cardiovascular – *Frequent*: tachycardia; postural hypotension, hypotension. *Infrequent*: hypertension; bradycardia, edema (extremities), angina pectoris, extrasystoles, cardiac failure, flushing, myocardial infarction, cerebrovascular accident, myocardial ischemia. *Rare*: transient ischemic attack, phlebitis, atrial fibrillation, cardiac arrest, bundle branch block. Central and Peripheral Nervous System Disorders – *Frequent*: paresthesia, migraine. *Infrequent*: hyperkinesia, vertigo, hypertonia, extrapyramidal disorder, leg cramps, involuntary muscle contractions, hypokinesia, neuralgia, dystonia, abnormal gait, hypesthesia, ataxia. *Rare*: abnormal coordination, hyperesthesia, ptosis, stupor. Endocrine Disorders – *Rare*: hypothyroidism, goiter, gynecomastia. Gastrointestinal Disorders – *Frequent*: saliva increased, flatulence. *Infrequent*: gastritis, gastroenteritis, stomatitis, eructation, hemorrhoids, dysphagia, teeth grinding, gingivitis, esophagitis. *Rare*: colitis, gastric ulcer, cholecystitis, cholelithiasis, duodenal ulcer, gastroesophageal reflux, glossitis, jaundice, diverticulitis, rectal hemorrhage, hiccups. General – *Infrequent*: hot flushes, rigors, alcohol intolerance, syncope, influenza-like symptoms. *Rare*: hayfever. Hemic and Lymphatic Disorders – *Infrequent*: purpura, anemia, epistaxis, leukocytosis, leucopenia, lymphadenopathy. *Rare*: pulmonary embolism, granulocytopenia, lymphocytosis, lymphopenia, hypochromic anemia, coagulation disorder, gingival bleeding. Metabolic and Nutritional Disorders – *Frequent*: decreased weight, increased weight. *Infrequent*: increased hepatic enzymes, thirst, dry eyes, increased alkaline phosphatase, abnormal glucose tolerance. *Rare*: bilirubinemia, hypokalemia, obesity, hypoglycemia, hepatitis, dehydration. Musculoskeletal System Disorders – *Infrequent*: arthritis, muscle weakness, skeletal pain. *Rare*: bursitis, osteoporosis. Psychiatric Disorders – *Frequent*: impaired concentration, amnesia, apathy, depression, increased appetite, aggravated depression, suicide attempt, confusion. *Infrequent*: increased libido, aggressive reaction, paroniria, drug dependence, depersonalization, hallucination, euphoria, psychotic depression, delusion, paranoid reaction, emotional lability, panic reaction, psychosis. *Rare*: catatonic reaction, melancholia. Reproductive Disorders,Female* – *Frequent*: amenorrhea. *Infrequent*: galactorrhea, breast pain, breast enlargement, vaginal hemorrhage. *%, based on female subjects only: 2955 Respiratory System Disorders – *Frequent*: coughing. *Infrequent*: bronchitis, dyspnea, pneumonia. *Rare*: asthma, laryngitis, bronchospasm, pneumonitis, sputum increased. Skin and Appendages Disorders – *Frequent*: rash, pruritus. *Infrequent*: photosensitivity reaction, urticaria, acne, skin discoloration, eczema, alopecia, dermatitis, skin dry, psoriasis. *Rare*: hypertrichosis, decreased sweating, melanosis, keratitis, cellulitis, pruritus ani. Special Senses – *Frequent*: accommodation abnormal, taste perversion. *Infrequent*: tinnitus, conjunctivitis, eye pain. *Rare*: mydriasis, photophobia, diplopia, abnormal lacrimation, cataract, taste loss. Urinary System Disorders – *Frequent*: polyuria. *Infrequent*: micturition frequency, urinary incontinence, urinary retention, dysuria. *Rare*: facial edema, hematuria, oliguria, pyelonephritis, renal calculus, renal pain. **OVERDOSAGE Human Experience** Although there were no reports of fatal citalopram overdose in clinical trials involving overdoses of up to 2000 mg, postmarketing reports of drug overdoses involving citalopram have included 12 fatalities, 10 in combination with other drugs and/or alcohol and 2 with citalopram alone (3920 mg and 2800 mg), as well as nonfatal overdoses of up to 6000 mg. Symptoms most often accompanying citalopram overdose, alone or in combination with other drugs and/or alcohol, included dizziness, sweating, nausea, vomiting, tremor, somnolence, and sinus tachycardia. In more rare cases, observed symptoms included amnesia, confusion, coma, convulsions, hyperventilation, cyanosis, rhabdomyolysis, and ECG changes (including QTc prolongation, nodal rhythm, ventricular arrhythmia, and one possible case of Torsades de pointes).

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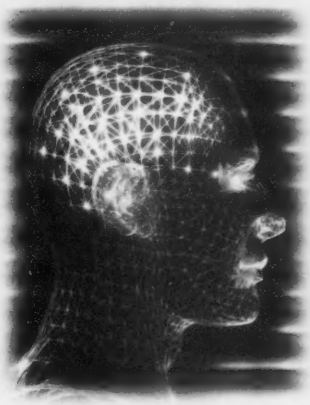
CME 2002 The Brain

Brain function in aging: Solutions for significant challenges

One of the greatest fears associated with aging is decline that undermines normal mental and physical function. Older persons intuitively understand that with this loss comes loss of independence and, sometimes, loss of the self. For adults who look forward to their "golden years," this potential for mental and functional decline casts an unsettling shadow.

Neurologic and psychiatric disorders play a significant role in contributing to this decline, and management of such decline can be a formidable task for primary care physicians. Indeed, brain disorders—dementia, Alzheimer's and Parkinson's disease, stroke, depression, and delirium—are among the most challenging clinical conditions for physicians caring for older persons.

The situation is made more challenging by the burgeoning geriatric population. Since 1900, the percentage of Americans age 65 and older has more than tripled (4.1% in 1900 to 12.7% in 1999). In 1999, persons aged 65 and older numbered 34.5 million. By 2030, there will be approximately 70 million older persons. Moreover, the number of persons in the older age ranges is growing significantly. For example, compared with 1900, in 1999 the 75 to 84 group (12.1 million) was 16 times larger and the 85+ group (4.2 million) was 34 times larger.



Fortunately, in addition to living longer, Americans are maintaining good physical health well into their 80s and beyond. But with longevity comes increased risk for potentially debilitating neurologic and psychiatric conditions. Such conditions may stem from vascular disease or involve degenerative disorders that affect brain tissue.

In the 2002 CME series, Geriatrics turns its focus to the brain. The objective of this series is to familiarize physicians involved in geriatric primary care with the common neurologic and psychiatric disorders of aging. During the next 12 months, our CME contributing authors will address the diagnosis and management of brain disorders that impair quality of life of the aged and challenge the skills of the primary care physician. In addition to the conditions mentioned above, the series also will examine epilepsy, delirium and anxiety, tremor, neuropathic pain, sleep disorders, and substance abuse. Many of these conditions have a significant impact on geriatric quality of life:

- In the United States, stroke is the leading cause of disability and the third-leading cause of death among the aged. Vascular disease contributes to cognitive decline in older persons, even without overt signs of neurologic deficit.
- The cognitive decline associated with dementia and Alzheimer's disease is an ever-growing threat to older persons, undermining independence, familial and social relationships, nutrition, activities of daily living, and overall well-being.
- Some older persons presume that loneliness, loss of identity, and dependence are inevitable. This outlook can be exacerbated by anxiety, depression, delirium, and substance abuse.
- Older persons are at high risk for movement disorders and physical disability associated with tremor and Parkinson's disease, both of which can limit activities of daily living and discourage social contact.
- Sleep disorders, common among older persons, interfere with quality of life and cognitive function.
- Older patients are prone to neuropathic pain syndromes resulting primarily from physical traumas incurred during the course of a long life span.

Reading the series will help physicians develop a sufficient understanding of uncomplicated geriatric neurologic and psychiatric conditions—how to diagnose and treat them and how to recognize when referral to a specialist is indicated. With appropriate management of these conditions, the quality and length of life of your older patients can be improved and extended.

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Stroke and TIA

Prevention and management of cerebrovascular events in primary care

Jesse Weinberger, MD

Stroke is a major cause of death and disability in the United States. Control of risk factors—particularly hypertension, diabetes, elevated serum lipids, and atrial fibrillation—can significantly reduce the incidence of stroke. Platelet antiaggregant therapy has a role in primary and secondary stroke prevention. Patients with transient ischemic attacks presenting with carotid stenosis >70% can be managed surgically, whereas those with less stenosis can be treated with platelet antiaggregant therapy. Acute stroke is a medical emergency. Thrombolytic therapy with tissue plasminogen activator within 3 hours of event onset can significantly improve outcomes in selected ischemic stroke patients. Patients with intracerebral hemorrhage usually present with acute onset of identifiable neurologic deficits.

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Stroke is the third leading cause of death in the United States and is the leading cause of neurologic disability. In general, stroke is a disease of older persons. The incidence in persons under age 65 is less than 2 per 1,000 annually. But the incidence increases with age for men and women respectively: 4.6 and 3.8 per 1,000 for ages 65 to 74; 9.4 and 7.4 for ages 75 to 84.[1] Persons with a history of transient ischemic attacks (TIAs) and atrial fibrillation are at increased risk for stroke.

This article reviews the pharmacologic and surgical approaches for reducing the risk of stroke and managing emergent events. Included are discussions of management of atrial fibrillation and TIA. The article also explores the role of antithrombotic therapy in stroke prevention and management, and management of acute ischemic stroke—within the 3-hour treatment window—with thrombolytic therapy. A brief section on hemmorrhagic stroke includes a discussion of subarachnoid hemorrhage. A table summarizes the management considerations and interventions for patients at high risk for stroke; subsequent tables summarize antiaggregant treatment for stroke prevention and management of carotid stenosis.

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Etiology

Ischemic strokes, caused by occlusion of an artery, account for 80 to 85% of cerebrovascular events, whereas hemorrhagic strokes, caused by a ruptured artery, account for 15 to 20%.[2]

There are three main causes of ischemic stroke:

- atherosclerotic disease of large extracranial and intracranial vessels
- occlusion of intracranial vessels by emboli from a cardiac source (cardioembolic stroke)
- and small vessel intracranial occlusive disease resulting from hypertension and diabetes.

To help prevent stroke occurrence, the most important contribution the internist or family practitioner can make is to help older patients modify controllable risk factors, particularly hypertension, diabetes, and serum lipids. The practitioner also should recognize when a patient is experiencing warning signs of impending stroke or TIA and refer patients to a neurologist for appropriate management.

Patients should understand that stroke requires emergency medical treatment within 3 hours of onset for

best outcomes. Patients who suspect they are having a stroke should call 911 and proceed directly to a hospital emergency department, preferably where they can be met by their primary care physician. Within the 3-hour window, a neurologist (preferably a stroke specialist) should be consulted immediately to help determine whether thrombolytic therapy is appropriate.

Patient assessment

All older patients should be evaluated for stroke risk factors (table 1). A careful history and physical examination should be performed. In addition to hypertension, diabetes, and smoking, other significant risk factors for stroke include atrial fibrillation, carotid artery stenosis, and history of TIA. Patients should be asked if they have ever experienced warning signs of stroke, such as transient weakness of the right face, arm and leg; numbness in the extremities; slurred speech; or unilateral vision loss.

Assessment also should include:

- regular blood pressure checks at the time of routine physical examination
- Auscultation of the neck and chest to check for carotid artery bruit and heart murmur (suggestive of valvular heart disease)
- electrocardiography, which can identify cardiac arrhythmias such as atrial fibrillation (a cause of cardioembolic stroke)
- serum lipid profiling
- questions about smoking history.

Atrial fibrillation and anticoagulation

Cardiogenic embolization, particularly when associated with nonvalvular atrial fibrillation, is a significant stroke risk factor in older persons. Risk of stroke from untreated nonvalvular atrial fibrillation is 5% per year in patients over age 70.[3]

Anticoagulation with warfarin (Coumadin) in these patients can reduce stroke risk by 70%, whereas platelet antiaggregant therapy using aspirin reduces the risk by 20%.[4] Patients under age 70 with atrial fibrillation but no other associated heart disease can get effective stroke prophylaxis with aspirin, 325 mg/d. Stroke prophylaxis guidelines for patients over age 70 who have nonvalvular atrial fibrillation recommend warfarin administration that achieves a target INR of 2.5 (or within the range of 2.0 to 2.9).[4]

Patients over age 85 are at greater risk for complications of cerebral hemorrhage when anticoagulated with warfarin, therefore their target INR should be kept close to 2.0. In patients with atrial fibrillation and mitral stenosis and those with mechanical cardiac valve replacement, anticoagulation should achieve a target INR range of 3.0 to 3.5.[5]

Anticoagulation with warfarin is beneficial as stroke prophylaxis during the first 3 months after an MI; it is particularly useful in patients with large anterior wall infarction and akinetic wall segments.[6] (For the study cited, age was not an independent risk factor.)

Carotid artery bruit. Patients with asymptomatic carotid artery stenosis can be identified by auscultation of a carotid artery bruit near the angle of the jaw. Whether management of patients with asymptomatic carotid artery stenosis should consist of surgical or medical therapy requires further study. Table 2 summarizes the management of patients with carotid stenosis. In a controlled trial involving asymptomatic patients with >60%

Table 1 Ischemic stroke: Checklist for patient management

Review risk factors
Hypertension
Diabetes
Poor diet; no exercise
High serum cholesterol
Smoking
Atrial fibrillation
Carotid stenosis (TIA history)
Patient assessment
History and physical exam
Is patient high-risk? (eg, has one or more of the risk factors above)
If high-risk, check for TIA history or TIA risk (auscultation, Doppler studies)
Rule out atrial fibrillation
Primary prevention
Patient education regarding stroke symptoms, signs
Risk-factor management
Maintain normotension
Tight glycemic control
Cholesterol lowering
Diet modification; exercise
Antithrombotic therapy (platelet antiaggregant therapy)
Primary/secondary prevention
Pharmacologic management of cardiac risk factors (eg, atrial fibrillation, post MI)
Antithrombotic therapy (platelet antiaggregant therapy, anticoagulation)
Surgical intervention*
Endarterectomy
Stent placement

* Consider for select patients

Source: Prepared for Geriatrics by Jesse Weinberger, MD

Table 2 Stroke prevention in patients with carotid stenosis

Patient	Degree of stenosis	Treatment
Asymptomatic (identified by carotid artery bruit)†‡	<60%	Antiaggregant therapy*
	>60%	Consider endarterectomy
History of TIA†§	0 to 40%	Antiaggregant therapy*
	50 to 69%	Antiaggregant therapy*; endarterectomy in selected cases
	70 to 99%	Endarterectomy (or stenting in high-risk patients), unless significant contraindications exist

TIA: Transient ischemic attack
* See table 3
† Stenosis as measured by duplex Doppler sonograph
‡ For patients who meet criteria of Asymptomatic Carotic Atherosclerosis Study (ACAS)
§ For patients who meet criteria of North American Symptomatic Carotid Endarterectomy Trail (NASCET)

Source: Prepared with data obtained from references 7 and 8.

stenosis of the carotid, the aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was estimated to be 5.1% for patients who underwent carotid endarterectomy and 11% for patients treated with daily aspirin and medical risk factor management.[7]

Patients in whom asymptomatic cervical bruit is detected can be screened noninvasively with duplex Doppler ultrasonography to assess the degree of carotid stenosis. Patients with severe stenosis (>60%) can be considered for surgical management if there are no significant medical risks to surgery, such as severe coronary artery disease or congestive heart failure. Patients who have moderate stenosis (<60%) or are not surgical candidates should receive platelet antiaggregant therapy with aspirin, ticlopidine (Ticlid), clopidogrel (Plavix), or combination aspirin/dipyridamole (Aggrenox). Diet or statin therapy is recommended for these patients if cholesterol levels exceed 230 mg/dL. Table 3 summarizes medical management with antiaggregant therapy.

Management of TIAs

Patients who experience TIAs and the associated transient symptoms—difficulty with speech, sudden weakness or numbness of the extremities, loss of balance, visual disturbance—are at increased risk for stroke. Without stroke prophylaxis, these patients have a 25 to 50% chance of experiencing a subsequent stroke that causes permanent neurologic deficits.[2] Stroke is most likely to occur in the first 3 months after a TIA.[8]

Aspirin. The original study demonstrating a beneficial effect of aspirin in prevention of stroke for patients with TIA found that a dosage of 650 mg bid reduced the stroke rate by 50%. However, there was no significant reduction in the stroke rate for women in this trial.[9] This prompted several subsequent trials that investigated lower dosages of aspirin (50 to 325 mg/d); results from these showed beneficial reduction of stroke in men and women,[10] although to a lesser extent than the original study. A comparison of individual aspirin trials showed that in patients with TIA, a higher dose of aspirin (at least 975 mg/d) is more effective in preventing stroke than a lower dose.[11]

Aspirin/dipyridamole. The European Stroke Prevention Study underscored the benefits of combination anti-platelet therapy.[3] In this trial, the combination antiplatelet agent aspirin/ dipyridamole, 400 mg/d, yielded the same efficacy in reduction of stroke as 50 mg/d aspirin; in previous trials, aspirin/dipyridamole alone showed no beneficial effect in preventing stroke in TIA patients. Compared with placebo, aspirin/dipyridamole reduced the rate of stroke by 37% in patients with a history of stroke or TIA. The efficacy of aspirin/dipyridamole has not been compared with a higher dosage of aspirin.

Ticlopidine. The antiplatelet agent ticlopidine was developed for patients who cannot tolerate the GI side effects associated with aspirin. Clinical data showed that compared with aspirin, 1,300 mg/d, ticlopidine, 500 mg/d, provided a 12% risk reduction in fatal and nonfatal stroke in patients with a history of TIA.[12] Ticlopidine use, however, was associated with a significantly higher risk of complications (eg, diarrhea, peptic ulceration, gastritis, and GI bleeding) than aspirin. The authors concluded that ticlopidine was somewhat more effective than aspirin in preventing strokes in this population, but that the risks of side effects were greater.

Clopidogrel. The CAPRIE trial showed that long-term administration of clopidogrel, 75 mg/d, a platelet aggregation inhibitor similar to ticlopidine, is more effective than aspirin in reducing the combined risk of ischemic stroke, MI, and vascular death in patients with atherosclerosis.[13] Compared with clopidogrel alone, aspirin, 75 to 325 mg/d, and clopidogrel, 75 mg/d produced a further reduction of 20% in vascular events in patients with acute coronary syndromes.

Clopidogrel, 75 mg/d, is now preferred over ticlopidine for treatment of patients with TIA who cannot tolerate aspirin or who have recurrent vascular events while on aspirin therapy. Ticlopidine, 250 mg bid, is still an effective option, but biweekly laboratory testing must be used for the first 3 months of administration to rule out hematologic and hepatic side effects. Ticlopidine administration is associated with neutropenia (2% of pa-

tients), hepatitis (0.4%), and thrombocytopenic purpura (1 case per 1,600 to 5,000).

Patients in whom carotid artery stenosis is not the cause of TIA should undergo transesophageal echocardiography to rule out a source of emboli from fibrin clots in the heart. Patients with TIA who have patent foramen ovale, atrial septal aneurysm, or dilated cardiomyopathy with a ventricular clot must be treated with warfarin rather than with platelet antiaggregant therapy. Platelet antiaggregant therapy is ineffective in preventing further fibrin clots from forming in the heart, whereas warfarin prevents cardioembolic stroke in these patients.[2] When a cerebral ischemic event is not caused by a cardioembolic source, warfarin confers no beneficial effect in prevention of stroke over aspirin.[14]

Carotid stenosis. Approximately one-half of patients with TIA exhibit >50% stenosis at the bifurcation of the cervical carotid artery. The definitive test for measuring the degree of carotid stenosis is catheter angiography, but this procedure is associated with a 1% incidence of stroke or death in patients with atherosclerotic or cerebrovascular disease.

Imaging. Noninvasive imaging of the carotid bifurcation can be performed with duplex Doppler ultrasonography, magnetic resonance angiography (MRA), or CT angiography. Compared with catheter angiography, which is considered the definitive method for identifying the degree of carotid stenosis, duplex Doppler ultrasonography and MRA have a 90% accuracy rate. Combining the two imaging approaches achieves accuracy virtually on par with catheter angiography.

Patients with TIA are usually initially examined with duplex Doppler ultrasonography. If results show stenosis >70% or if the examiner does not consider the results to be definitive, MRA is performed to confirm the duplex Doppler ultrasonography findings.[15]

MRA cannot be performed on patients with pacemakers or who are claustrophobic; these patients should undergo CT angiography. Although this procedure also yields 90% accuracy, the process requires injection of a large volume of contrast dye, so it may be contraindicated in patients with congestive heart failure or renal disease.

Table 3 Antiaggregant therapy for prevention of stroke*

Agent	Dosage
Aspirin	50 mg/d to 650 mg bid
Ticlopidine (Ticlid)	200 mg bid
Clopidogrel (Plavix)	75 mg/d
Aspirin/dipyridamole (Aggrenox)	25/100 mg bid

*For patients at risk of stroke and not scheduled for surgical intervention

Source: Prepared with data obtained from references 3, 9, 10, 12, 13.

Surgical intervention

Endarterectomy. Patients with carotid stenosis >70% may benefit from carotid endarterectomy. At centers where the complication rate for endarterectomy is <2%, the intervention can reduce the risk of subsequent stroke from 25 to 5% in patients on aspirin therapy.[16]

Patients exhibiting <50% carotid stenosis do not benefit from carotid endarterectomy and instead should be on medical therapy with aspirin, clopidogrel, or aspirin/dipyridamole. Some patients exhibiting carotid stenosis between 50 to 70% may benefit from endarterectomy rather than medical therapy; they should be referred to a stroke neurology consultant.

Stent placement. For older patients who are not endarterectomy candidates, carotid artery stent placement is an option. The risk of stroke during the procedure is similar to that of carotid endarterectomy (2 to 8% depending on the center), but the systemic complications are reduced.[17]

Management of acute ischemic stroke

An acute ischemic stroke is a medical emergency, and patients need immediate attention. When possible, the primary care physician should collaborate with the stroke team on emergency intervention. Acute medical care includes stabilizing a patient's cardiopulmonary status and determining whether the stroke was accompanied by an acute MI or respiratory distress.

Blood pressure should be carefully monitored. If the patient is hypotensive, raising the blood pressure may improve the condition. In general, hypertension associated with acute stroke is not treated so that perfusion to the ischemic area will not be reduced unless the mean arterial pressure is >140 mm Hg. Even in this scenario, blood pressure is reduced gradually, usually with low doses of IV labetalol HCl (Normodyne). Acute reduction of the blood pressure can worsen the neurologic symptoms.[18]

Patient assessment. CT should be among the first tests performed on patients suspected of having a stroke. Results will rule out a hemorrhagic event or reveal early signs of permanent infarction, which can increase the risk of hemorrhagic complications.

The stroke neurologist should use the NIH Stroke Scale to quantify the severity of the event. Patients in good condition (a score <5) will not benefit from thrombolytic therapy; patients with severe strokes (a score of >25) are at high risk for hemorrhagic complications and should not receive thrombolytic therapy. Thrombolytic therapy is used only in patients with no hemorrhage or signs of early infarction on the initial CT performed within 3 hours of the event.

tPA. Thrombolytic therapy with tissue plasminogen activator (tPA) should be administered to patients with acute ischemic stroke who are medically stable and can be treated within 3 hours of stroke onset. Throm-

bolytic intervention improves the patient's likelihood of returning to excellent status 3 months after the event (21% for untreated patients, 31% for treated patients).[19] Moreover, age is not a limiting factor for administration of tPA. The risk of death from tPA-induced hemorrhage is 3%, but the intervention has not been shown to increase overall mortality. Hemorrhagic complications were higher in patients over age 85, but the rate was not statistically significant. [19]

Tissue plasminogen activator must be used judiciously and precisely to avoid hemorrhagic complications and death. This requires consultation with the stroke neurologist. Tissue plasminogen activator can be administered if:

- prothrombin time, partial thromboplastin time, and platelet count are not elevated
- the patient has no history of recent surgery or any other illness that could result in significant systemic bleeding.

If all criteria are met, IV tPA is administered at a rate of 0.9 mg/kg over 1 hour with 10% given as an initial bolus. Thrombolytic therapy can also be administered intra-arterially, increasing the therapeutic window to 6 hours, although not without the risk of hemorrhagic complications.

Patients who arrive after the 3-hour window should be evaluated to determine the etiology of the ischemic stroke. Patients who have experienced a stroke and have known cardioembolic sources—particularly atrial fibrillation—are at risk for recurrent stroke within 7 days of the initial event and should undergo prophylactic anticoagulation.

Anticoagulation

To avoid hemorrhage into the area of infarction, anticoagulation is not initiated until 48 hours after stroke onset. Initial treatment consists of administration of heparin with a target PTT of 50 to 70 (a bolus is not given). Alternatively, low-molecular weight heparin (enoxaparin [Lovenox]), 1 mg/kg, can be administered subcutaneously. Parenteral anticoagulation with oral warfarin therapy is maintained until a therapeutic INR of 2.0 to 3.0 has been achieved. In patients with massive infarction and edema, anticoagulation may be deferred until the edema resolves.[18]

Anticoagulation is effective in only a select group of ischemic stroke patients and should be used with care in older persons. Anticoagulation is necessary to prevent recurrent cardioembolic stroke from intracardiac fibrin thrombus due to atrial fibrillation, patent foramen ovale, dilated cardiomyopathy, or valvular heart disease. Anticoagulation may also provide some benefit for patients with large vessel occlusive disease (eg, carotid or basilar artery occlusion) who are having progressive symptoms.[20]

Ischemic stroke patients not undergoing anticoagulation should receive acute platelet antiaggregant therapy with aspirin, which improves outcomes by 1%.[21] Given that 500,000 strokes occur annually in the United States, this is not insignificant improvement. Combining a bolus of clopidogrel, 75 mg, with aspirin, 81 or 325 mg, is 20% more effective than clopidogrel alone in preventing ischemic events in patients with unstable angina and may also be more beneficial in improving outcomes in stroke patients.[22]

Management of hemorrhagic stroke

Patients with intracerebral hemorrhage usually present with acute onset of neurologic deficits including:

- weakness of one side of the body associated with severe headache
- progressive depression of the level of consciousness.

Cerebral hemorrhage in the deep structures of the brain—caused by hypertension—is more common in younger patients; lobar hemorrhage in the cortex—caused by amyloid angiopathy—is more common in older adults.

Swift achievement of normotension (and avoidance of hypotension) should be the goal for patients who present with elevated blood pressure. If CT results reveal increased intracranial pressure or massive shift of brain structures, the patient should be treated with IV mannitol, 100 grams, administered over 1 hour. If the patient needs ventilatory assistance, mechanical hyperventilation should be used.

Steroid medications have not been proven to be effective in intracerebral hemorrhage. Surgical removal of intracerebral hematomas has not been beneficial except in the case of cerebellar hemorrhage.

Patients presenting with acute vertigo, headache, and imbalance with progressive lethargy should be evaluated immediately with CT to rule out cerebellar hemorrhage. In patients with lobar hemorrhage, brain MRI should be performed to rule out an underlying tumor, arteriovenous malformation, or cavernous angioma.[18]

Subarachnoid hemorrhage (SAH) occurs when there is rupture of a saccular aneurysm at branch points in the circle of Willis or as result of arterio-venous malformations. Patients present with severe headache and varying degrees of altered mental status or focal neurologic deficit. CT of the brain is performed to document the hemorrhage. If SAH is strongly suspected, lumbar puncture is performed if CT results are negative. Patients are treated with nimodipine (Nimotop), 60 mg, every 4 hours orally or by feeding tube.[23]

Patients are graded by the Hunt-Hess scale to determine their clinical condition. Patients with headache alone who are awake and alert are considered grade I. Patients with mild drowsiness or confusion or minimal focal deficits such as hemiparesis are grade II. Grade I and II patients can be considered for neurosurgical management to clip the aneurysm and prevent rebleeding. Grade III to V patients have increasing degrees of alteration of state of consciousness or focal deficit. These patients have poor outcomes with surgical management, and surgery is usually deferred unless their clinical condition improves.

Cerebral angiography should be performed to document the source of the bleeding. If an aneurysm is identified, surgical therapy within 24 hours after onset provides the most effective prevention of rebleeding without encountering ischemic consequences of vasospasm. After 24 hours, the risk for complications associated with surgery increases, and it is usually better to manage the patient conservatively for 14 days prior to surgical clipping of the aneurysm.[24]

Conclusion

Modification of controllable risk factors plays a significant role in reducing the risk of stroke. Physicians should work closely with patients to help precipitate behavioral and lifestyle changes and to encourage the use of appropriate pharmacologic therapies. Antithrombotic therapy should be used to reduce stroke risk in patients with atrial fibrillation and history of TIA. Patients with a history of TIA should undergo assessment for carotid stenosis and be considered for platelet antiaggregant and surgical therapy.

Swift intervention for acute ischemic stroke significantly improves post-stroke prognosis. Thrombolytic therapy with tPA must occur within 3 hours of event onset, although intra-arterial administration can increase the intervention window to 6 hours. Patients who have experienced a stroke and have known cardioembolic sources must be carefully managed to prevent recurrent stroke. Patient education also should be included in stroke prevention efforts. G

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Turn to page 44 to take the exam

CME Geriatrics Exam

Detach or photocopy this page, place an X in the boxes that correspond to your answers, fill in your name and address, and mail (see address below). Answers must be received by July 1, 2002. A score of at least 80% must be earned to receive CME credit.

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Weinberger J. Stroke and TIA: Prevention and management of cerebrovascular events in primary care. Geriatrics 2002; 57(Jan):38-43.

1. Approximately one-half of patients with TIA exhibit what percentage of stenosis at the bifurcation of the cervical carotid artery.
   - ☐ a. <50
   - ☐ b. >50
   - ☐ c. <40
   - ☐ d. >40
2. Patients with carotid stenosis of what percentage may benefit from carotid endarterectomy.
   - ☐ a. >40
   - ☐ b. >50
   - ☐ c. >60
   - ☐ d. >70
3. Medical therapy for stroke prevention involves which of the following:
   - ☐ a. ticlopidine
   - ☐ b. clopidogrel
   - ☐ c. aspirin
   - ☐ d. all of the above
4. Patients in whom carotid artery stenosis is not the cause of TIA should undergo transesophageal echocardiography to rule out a source of:
   - ☐ a. emboli from fibrin clots in the heart
   - ☐ b. emboli at angle of the jaw
   - ☐ c. emboli from fibrin clots in the lungs
   - ☐ d. none of the above
5. Cardiogenic embolization, particularly when associated with nonvalvular atrial fibrillation, is a significant stroke risk factor in older persons
   - ☐ a. True ☐ b. False
6. Patients under age 70 with atrial fibrillation but no other associated heart disease can get effective stroke prophylaxis with daily intake of:
   - ☐ a. warfarin
   - ☐ b. aspirin
   - ☐ c. vitamins
   - ☐ d. tissue plasminogen activator (tPA)
7. Thrombolytic therapy with tPA should be administered to patients with acute ischemic stroke who are medically stable and can be treated within how many hours of stroke onset:
   - ☐ a. 6
   - ☐ b. 5
   - ☐ c. 4
   - ☐ d. 3
8. To avoid hemorrhage into the area of infarction, anticoagulation is not initiated until how many hours after ischemic stroke onset:
   - ☐ a. 48
   - ☐ b. 36
   - ☐ c. 24
   - ☐ d. 12

In addition to the exam questions, answer the following evaulation questions: (1=strongly agree, 6=strongly disagree)

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   1 2 3 4 5 6
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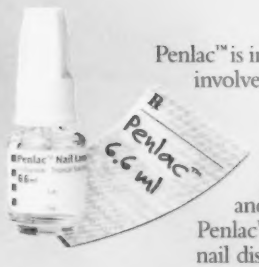

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1. IMS Data. September 2001.
2. Penlac [prescribing information]. August 2000.

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PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, as a component of a comprehensive management program, is indicated as topical treatment in immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails without lunula involvement, due to *Trichophyton rubrum*. The comprehensive management program includes removal of the unattached, infected nails as frequently as monthly, by a health care professional who has special competence in the diagnosis and treatment of nail disorders, including minor nail procedures.

- No studies have been conducted to determine whether ciclopirox might reduce the effectiveness of systemic antifungal agents for onychomycosis. Therefore, the concomitant use of 8% ciclopirox topical solution and systemic antifungal agents for onychomycosis, is not recommended.
- PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should be used only under medical supervision as described above.
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- The safety and efficacy of using PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, daily for greater than 48 weeks have not been established.

Clinical Trials Data
The results of use of PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, in treatment of onychomycosis of the toenail without lunula involvement were obtained from two double-blind, placebo-controlled studies conducted in the US. In these studies, patients with onychomycosis of the great toenails without lunula involvement were treated with ciclopirox topical solution, 8%, in conjunction with monthly removal of the unattached, infected toenail by the investigator. PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, was applied for 48 weeks. At baseline, patients had 20-65% involvement of the target great toenail plate. Statistical significance was demonstrated in one of two studies for the endpoint "complete cure" (clear nail and negative mycology), and in two studies for the endpoint "almost clear" (≤10% nail involvement and negative mycology) at the end of study. These results are presented below.

At Week 48 (plus Last Observation Carried Forward) for the Intent-to-Treat (ITT) Population

	Study 312		Study 313	
	Active	Vehicle	Active	Vehicle
Complete Cure* (0%)	6/110 (5.5%)	1/109 (0.9%)	10/118 (8.5%)	0 / 1 1 7
Almost Clear** (0.9%)	7/107 (6.5%)	1/108 (0.9%)	14/116 (12%)	1 / 1 1 5
Negative Mycology Alone*** (9%)	30/105 (29%)	12/106 (11%)	41/115 (36%)	1 0 / 1 1 4

* Clear nail and negative mycology
** ≤10% nail involvement and negative mycology
*** Negative KOH and negative culture

The summary of reported patient outcomes for the ITT population at 12 weeks following the end of treatment are presented below. Note that post-treatment efficacy assessments were scheduled only for patients who achieved a complete cure.

Post-treatment Week 12 Data for Patients Who Achieved Complete Cure at Week 48

	Study 312		Study 313	
	Active	Vehicle	Active	
Vehicle				
Number of Treated Patients 118	112	111	119	
Complete Cure at Week 48	6	1	10	0
Post-treatment Week 12 Outcomes:				
Patients Missing All Week 12 Assessments	2	0	2	0
Patients with Week 12 Assessments	4	1	8	0
Complete Cure	3	1	4	0
Almost Clear	2*	1	1*	0
Negative Mycology	3	1	5	0

*Four patients (from studies 312 and 313) who were completely cured did not have post-treatment Week 12 planimetry data.

CONTRAINDICATIONS
PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, is contraindicated in individuals who have shown hypersensitivity to any of its components.

WARNINGS
PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, is not for ophthalmic, oral, or intravaginal use. For use on nails and immediately adjacent skin only.

PRECAUTIONS
If a reaction suggesting sensitivity or chemical irritation should occur with the use of PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, treatment should be discontinued and appropriate therapy instituted.
So far there is no relevant clinical experience with patients with insulin dependent diabetes or who have diabetic neuropathy. The risk of removal of the unattached, infected nail, by the health care professional and trimming by the patient, should be carefully considered before prescribing to patients with a history of insulin dependent diabetes mellitus or diabetic neuropathy.

Information for Patients
Patients should have detailed instructions regarding the use of PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, as a component of a comprehensive management program for onychomycosis in order to achieve maximum benefit with the use of this product.
The patient should be told to:

1. Use PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, as directed by a health care professional. Avoid contact with the eyes and mucous membranes. Contact with skin other than skin immediately surrounding the treated nail(s) should be avoided. PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, is for external use only.
2. PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should be applied evenly over the entire nail plate and 5 mm of surrounding skin. If possible, PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should be applied to the nail bed, hyponychium, and the under surface of the nail plate when it is free of the nail bed (e.g., onycholysis). Contact with the surrounding skin may produce mild, transient irritation (redness).
3. Removal of the unattached, infected nail, as frequently as monthly, by a health care professional is needed with use of this medication.
4. Inform a health care professional if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing).
5. Up to 48 weeks of daily applications with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, and professional removal of the unattached, infected nail, as frequently as monthly, are considered the full treatment needed to achieve a clear or almost clear nail (defined as 10% or less residual nail involvement).
6. Six months of therapy with professional removal of the unattached, infected nail may be required before initial improvement of symptoms is noticed.
7. A completely clear nail may not be achieved with use of this medication. In clinical studies less than 12% of patients were able to achieve either a completely clear or almost clear toenail.
8. Do not use the medication for any disorder other than that for which it is prescribed.
9. Do not use nail polish or other nail cosmetic products on the treated nails.
10. Avoid use near heat or open flame, because product is flammable.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity study was conducted with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, formulation. A carcinogenicity study of ciclopirox (1% and 5% solutions in polyethylene glycol 400) in female mice dosed topically twice per week for 50 weeks followed by a 6-month drug-free observation period prior to necropsy revealed no evidence of tumors at the application sites.
In human systemic tolerability studies following daily application (~340 mg of PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%) in subjects with distal subungual onychomycosis, the average maximal serum level of ciclopirox was 31±28 ng/mL after two months of once daily applications. This level was 159 times lower than the lowest toxic dose and 115 times lower than the highest nontoxic dose in rats and dogs fed 7.7 and 23.1 mg ciclopirox (as ciclopirox olamine)/kg/day.
The following *in vitro* genotoxicity tests have been conducted with ciclopirox: evaluation of gene mutation in Ames *Salmonella* and *E. coli* assays (negative); chromosome aberration assays in V79 Chinese hamster lung fibroblasts, with and without metabolic activation (positive); gene mutation assay in the HGPRT-test with V79 Chinese hamster lung fibroblasts (negative); unscheduled DNA synthesis in human A549 cells (negative); and BALB/c3T3 cell transformation assay (negative). In an *in vivo* Chinese hamster bone marrow cytogenetic assay, ciclopirox was negative for chromosome aberrations at 5,000 mg/kg.
The following *in vitro* genotoxicity tests were conducted with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%: Ames Salmonella test (negative); unscheduled DNA synthesis in the rat hepatocytes (negative); cell transformation assay in BALB/c3T3 cell assay (positive). The positive response of the lacquer formulation in the BALB/c3T3 test was attributed to its butyl monoester of poly(methylvanyl ether/maleic acid) resin component (Gantrez® ES-435), which also tested positive in this test. The cell transformation assay may have been confounded because of the film-forming nature of the resin. Gantrez® ES-435 tested nonmutagenic in both the *in vitro* mouse lymphoma forward mutation assay with or without activation and unscheduled DNA synthesis assay in rat hepatocytes.
Oral reproduction studies in rats at doses up to 3.85 mg ciclopirox (as ciclopirox olamine)/kg/day [equivalent to approximately 1.4 times the potential exposure at the maximum recommended human topical dose (MRHTD)] did not reveal any specific effects on fertility or other reproductive parameters. MRHTD (mg/m2) is based on the assumption of 100% systemic absorption of 27.12 mg ciclopirox (~340 mg PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%) that will cover all the fingernails and toenails including 5 mm proximal and lateral fold area plus onycholysis to a maximal extent of 50%.

Pregnancy
Teratogenic effects: Pregnancy Category B
Teratology studies in mice, rats, rabbits, and monkeys at oral doses of up to 77, 23, 23, or 38.5 mg, respectively, of ciclopirox as ciclopirox olamine/kg/day (14, 8, 17, and 28 times MRHTD), or in rats and rabbits receiving topical doses of up to 92.4 and 77 mg/kg/day, respectively (33 and 55 times MRHTD), did not indicate any significant fetal malformations.
There are no adequate or well-controlled studies of topically applied ciclopirox in pregnant women. PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

Geriatric Use
Clinical studies of PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients.

ADVERSE REACTIONS
In the vehicle-controlled clinical trials conducted in the US, 9% (30/327) of patients treated with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, and 7% (23/328) of patients treated with vehicle reported treatment-emergent adverse events (TEAE) considered by the investigator to be causally related to the test material.
The incidence of these adverse events, within each body system, was similar between the treatment groups except for Skin and Appendages: 8% (27/327) and 4% (14/328) of subjects in the ciclopirox and vehicle groups reported at least one adverse event, respectively.
The most common were rash-related adverse events: periungual erythema and erythema of the proximal nail fold were reported more frequently in patients treated with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, (5% [16/327]) than in patients treated with vehicle (1% [3/328]). Other TEAEs thought to be causally related included nail disorders such as shape change, irritation, ingrown toenail, and discoloration.
The incidence of nail disorders was similar between the treatment groups. (2% [6/327] in the PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, group and 2% [7/328] in the vehicle group). Moreover, application site reactions and/or burning of the skin occurred in 1% of patients treated with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, (3/327) and vehicle (4/328).
A 21-Day Cumulative Irritancy study was conducted under conditions of semi-occlusion. Mild reactions were seen in 46% of patients with the PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, 32% with the vehicle and 2% with the negative control, but all were reactions of mild transient erythema. There was no evidence of allergic contact sensitization for either the PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, or the vehicle base. In the vehicle-controlled studies, one patient treated with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, discontinued treatment due to a rash, localized to the palm (causal relation to test material undetermined).
Use of PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, for 48 additional weeks was evaluated in an open-label extension study conducted in patients previously treated in the vehicle-controlled studies. Three percent (9/281) of subjects treated with PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, experienced at least one TEAE that the investigator thought was causally related to the test material. Mild rash in the form of periungual erythema (1% [2/281]) and nail disorders (1% [4/281]) were the most frequently reported. Four patients discontinued because of TEAEs. Two of the four had events considered to be related to test material: one patient's great toenail "broke away" and another had an elevated creatine phosphokinase level on Day 1 (after 48 weeks of treatment with vehicle in the previous vehicle-controlled study).

DOSAGE AND ADMINISTRATION
PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should be used as a component of a comprehensive management program for onychomycosis. Removal of the unattached, infected nail, as frequently as monthly, by a health care professional, weekly trimming by the patient, and daily application of the medication are all integral parts of this therapy.

Nail Care By Health Care Professionals
Removal of the unattached, infected nail, as frequently as monthly, trimming of onycholytic nail, and filing of excess horny material should be performed by professionals trained in treatment of nail disorders.

Nail Care By Patient
Patients should file away (with emery board) loose nail material and trim nails, as required, every seven days after PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, is removed with alcohol.
PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should be applied once daily (preferably at bedtime or eight hours before washing) to all affected nails with the applicator brush provided. The PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should be applied evenly over the entire nail plate.
If possible, PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should be applied to the nail bed, hyponychium, and the under surface of the nail plate when it is free of the nail bed (e.g., onycholysis).
The PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should not be removed on a daily basis. Daily applications should be made over the previous coat and removed with alcohol every seven days. This cycle should be repeated throughout the duration of therapy.

HOW SUPPLIED
PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, is supplied in 3.3 mL (NDC 0066-8008-01) and 6.6 mL (NDC 0066-8008-02) glass bottles with screw caps which are fitted with brushes.
Protect from light (e.g., store the bottle in the carton after every use).
PENLAC™ NAIL LACQUER (ciclopirox) Topical Solution, 8%, should be stored at room temperature between 59° and 86° F (15° and 30° C).
CAUTION: Flammable. Keep away from heat and flame.
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Gene D. Cohen, MD, PhD, Series Editor

Geriatrics is pleased to welcome Gene D. Cohen, MD, PhD, as "The Psychiatric Consultant" series editor for 2002. He is the author of more than 150 publications in the field of aging, including a book for the general public, "The Creative Age: Awakening Human Potential in the Second Half of Life," published in 2000 by Harper Collins/Avon Books. He was the primary investigator of a 25-year longitudinal study of ill older adults that evaluated problems ranging from depression and dementia to living independently in the community. During 1991-93, Dr. Cohen served as acting director of the National Institute on Aging. In this first article, he discusses his goals for the series and highlights some of the topics planned for this year.

During 2002, "The Psychiatric Consultant" column will broaden its focus on mental health and aging. In addition to presenting case examples on the treatment of mental illness in older patients, important aspects of promoting mental health in late life will be addressed. Interventions examined will include behavioral and psychosocial approaches as well as use of psychotropic medications.

In considering health and illness, it is important to recognize that the treatment issue is often not a health versus illness debate about where to clinically concentrate effort. Rather, many clinical situations provide opportunities to develop intervention plans that simultaneously address illness and health. Sometimes, the influence of mental health on physical health, and vice versa, is at work. In other cases, mental health and mental illness considerations coexist.

During the course of Alzheimer's disease, for example, patients experience a range of behavioral disturbances, such as agitation and wandering, as well as depression and delusions. Although pharmacologic interventions are available to alleviate these problems, nonpharmacologic approaches can be taken to structure patients' time and tap into their residual strengths, which in turn improves coping, decreases suffering, and enhances the dignity with which the patient and family traverse the course of this dread disease.

Next month's column will present a case example that sets the stage for a discussion of comprehensive treatment planning for Alzheimer's disease, including the roles of clinicians, family, and community services. Important online and toll-free resources will be included. The March column will build on this broad perspective, presenting a case example in which an innovative intergenerational approach is used to improve the quality of life of a patient and family dealing with Alzheimer's disease.

Dr. Cohen

The social portfolio

Meanwhile, what can physicians do about patients who come to the office concerned that, although their minds are functioning fine, their memories are not as sharp as they used to be? This question is not new to clinicians. Documentation from 1800 BC describes therapies made from internal organs of young animals to enhance the functioning of the aging

Dr. Cohen, a geriatric psychiatrist, is director of the Center on Aging, Health, & Humanities at George Washington University, Washington, DC, where he is professor of health care sciences and professor of psychiatry and behavioral sciences.

brain, body, and libido.[1] Similar promises for enhancing this age-old triad continue today, with a focus on hormones and alternative substances. Patients may ask about ginkgo biloba, DHEA, or other substances. The author of "The Definitive Book on DHEA" claims that DHEA will help you "grow younger . . . revitalize your sex life . . . enhance memory."[2] Upcoming articles in this column will discuss alternative approaches to mild memory and intellectual decline with aging.

Even in the absence of mild mental decline, there is a growing interest in what can be done to preserve mental functioning in later life and what strategies can be taken to prepare individuals for major transitions such as retirement. Most attention on retirement involves advice about economic security and obtaining good insurance coverage, with considerable emphasis on building a sound financial portfolio. Too little attention has been paid to developing a sound social portfolio. This issue deserves serious attention, not just in terms of its implications for quality of life, but also for health and longevity.

It is important to understand how patients might recover and cope when confronted with major mental or medical disorders

Glass et al illustrated the impact of socializing on health and longevity by comparing older persons involved in social and productive activities (ie, going to church, movies, restaurants, sporting events, as well as playing cards, participating in social groups, gardening, preparing meals, and volunteering) with those involved in physical fitness activities (ie, active sports, swimming, walking, or other physical exercise).[3] The point of the study was not to determine which type of activity provided more health benefits but to understand the underrecognized powerful and positive effects of social involvement and activity in late life. The researchers found that "social and productive activities that involve little or no enhancement of fitness lower the risk of all-cause mortality as much as fitness activities do. This suggests that in addition to increased cardiopulmonary fitness, [social or productive] activity may confer survival benefits through psychosocial pathways. Social and productive activities that require less physical exertion may complement exercise programmes and may constitute alternative intervention for elderly people."[3] Additional articles in this column will revisit this idea and focus on retirement planning in terms of developing a social portfolio for promoting mental health with aging.

Importance of hope

Related to this awareness of social and productive potential is the role hope plays in late life. Norman Cousins pointed out that "the human body experiences a powerful gravitational pull in the direction of hope. That is why the patient's hopes are the physician's secret weapon. They are the hidden ingredients in any prescription."[4] Hope becomes particularly important in the clinical setting when illness causes significant adversity in late life.

It is important from a mental health perspective to understand how patients might recover and cope when confronted with major mental or general medical disorders. Consider these examples of how older adults have learned to cope despite illness:

- William Carlos Williams was a poet and physician who practiced medicine into his 60s. He suffered a stroke at age 69 and was subsequently hospitalized for 1 year with depression. A decade later he published a book of poetry, "Pictures from Brueghel," for which he was awarded a Pulitzer Prize.
- Composer George Friederic Handel suffered a stroke at age 55 but went on to compose his great work, "Messiah," 5 years later.
- Grandma Moses lost her husband at age 67 and, in dealing with that loss, took up embroidery. Arthritis forced her to give up stitching 11 years later, but she discovered that she could paint despite her arthritic ailment. She began painting and eventually displayed her work in 15 international shows. She completed her last painting, "Rainbow," at age 101.

Later in this series, we will revisit the topic of potential in older adults and its clinical relevance. From these articles, you will learn to impart to your patients the lesson William Carlos Williams wrote about from personal experience—old age can add as it takes away.[5]

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Abstracts

A digest of recent research in geriatric care

Increased risk of CVD associated with high-normal BP

Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001; 345(Nov. 1):1291-7.

Patients with blood pressure (BP) at the high end of normal (130 to 139/85 to 89 mm Hg) may have an increased risk of developing cardiovascular disease, according to an analysis of data from the Framingham Heart Study.

Researchers conducted the study to investigate the relationship between cardiovascular disease and high-normal BP because information in this area is limited. They included 6,859 subjects (mean age 50) who did not have hypertension or prevalent cardiovascular disease at baseline. Subjects were classified into one of three categories based on their baseline BP measurements:

- optimal BP (systolic BP <120 mm Hg and diastolic BP <80 mm Hg)
- normal (systolic BP 120 to 129 mm Hg or diastolic BP 80 to 84 mm Hg)
- high-normal (systolic BP 130 to 139 mm Hg or diastolic BP 85 to 89 mm Hg).

If a patient's systolic and diastolic blood pressure readings belonged to two different categories, the higher reading was used to assign the patient to a category.

Primary outcome measures during 12-year follow-up were time to occurrence of MI, stroke, congestive heart failure (CHF), or death resulting from cardiovascular disease.

At baseline, one-quarter of the subjects had high-normal BP, one-third had normal BP, and the rest had optimal BP. More women than men had optimal (1,875 versus 1,005) and normal BP (1,126 versus 1,059), whereas more men than women had high-normal BP (903 versus 891). Subjects with high-normal BP were older, had higher serum cholesterol levels, and had a higher body-mass index compared with those who had optimal BP.

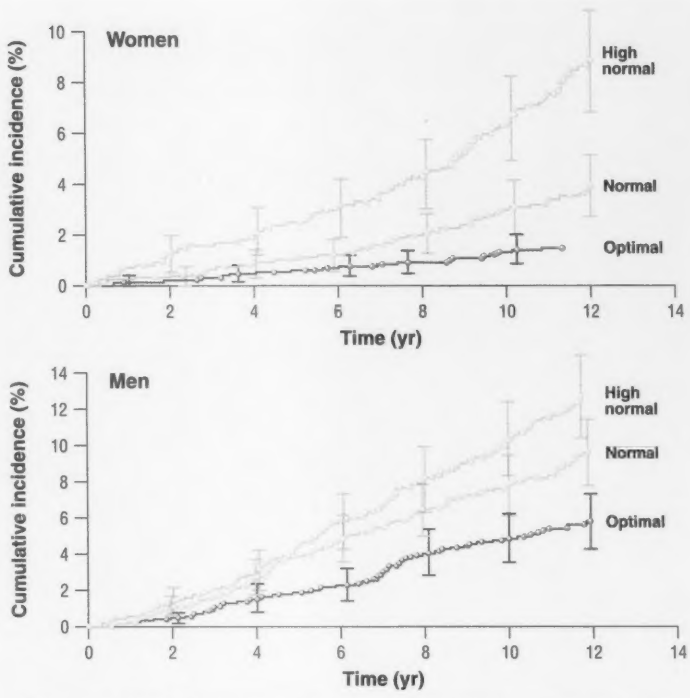

Figure. Cumulative incidence of cardiovascular events in women and men (mean age 50) without hypertension, according to blood-pressure category at the base-line examination. Vertical bars indicate 95% confidence intervals.

Source: N Engl J Med 2001; 345(Nov. 1):1295. Copyright © 2001 Massachusetts Medical Society. All rights reserved. Used with permission.

During follow-up, 397 of the 6,859 subjects experienced a first cardiovascular event, including 190 MIs, 85 strokes, 50 cases of CHF, and 72 deaths from cardiovascular disease. Rates of cardiovascular events increased with increasing blood pressure (figure). Compared with optimal BP, high-normal BP was associated with a hazard ratio (HR) for cardiovascular disease of 2.5 for women and 1.6 for men. Normal BP was associated with an HR of 1.5 for women and 1.3 for men when compared with optimal BP.

Among those age 35 to 64 with high-normal BP, the 10-year cumulative incidence of cardiovascular disease was 4% for women and 8% for men. Among those age 65 to 90 with high-normal BP, the 10-year cumulative incidence of cardiovascular disease was 18% for women and 25% for men.

The authors said additional research should be conducted to determine whether lowering high-normal BP would be beneficial for patients at high risk for cardiovascular disease.

continued

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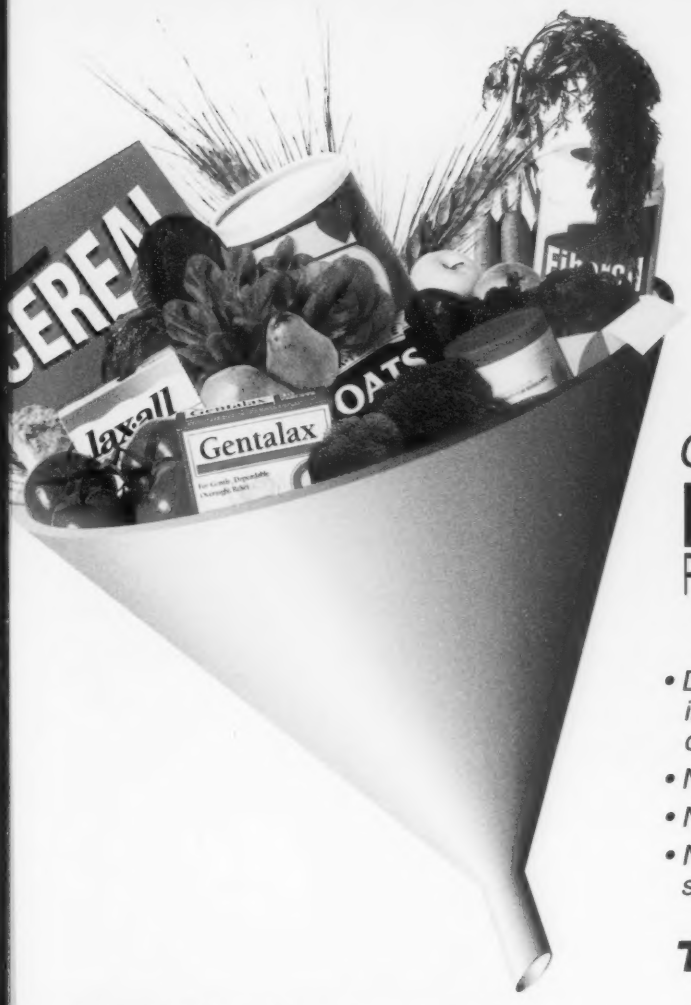

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BP medication may provide added benefit—preventing diabetes

Yusuf S, Gerstein H, Hoogwerf B, et al. Ramipril and the development of diabetes. JAMA 2001; 286(Oct. 17): 1882-5.

The angiotensin-converting enzyme (ACE) inhibitor ramipril appears to reduce the risk of developing diabetes in high-risk patients, according to investigators from the Heart Outcomes Prevention Evaluation (HOPE) trial.

Previous studies have shown benefits of ACE inhibitors over beta blockers and diuretics for lowering levels of hemoglobin A_{1c} (HbA_{1c}) and decreasing the risk of developing diabetes. The researchers evaluated a subgroup of patients from the HOPE study to investigate the effectiveness of ramipril in preventing diabetes among high-risk patients.

The subgroup included 5,720 patients (age 55 and older) who had no evidence of left ventricular dysfunction, heart failure, or diabetes but had vascular disease and one other cardiovascular risk factor. They were randomized to receive ramipril, up to 10 mg/d (2,837 patients), or placebo (2,883 patients). The primary outcome measure was a self-reported new diagnosis of diabetes during the mean 4.5 year follow-up. HbA_{1c} levels and medication use were recorded for those diagnosed with diabetes. HbA_{1c} values >110% of the upper limit of normal were considered a biochemical confirmation of diabetes.

By the end of the study, 102 subjects (3.6%) in the ramipril group reported a new diagnosis of diabetes compared with 155 subjects (5.4%) in the placebo group (relative risk [RR] 0.66). Compared with placebo, the RR in the ramipril group for having a new diagnosis of diabetes and an HbA_{1c} >110% was 0.60, for initiation of glucose-lowering therapy it was 0.56, and for both it was 0.51.

The authors said that although ramipril appears to reduce the risk of a new diagnosis of diabetes in high-risk patients, their results require confirmation because the findings could have significant clinical and public health implications. Therefore, they are initiating a large prospective trial to evaluate whether ramipril can prevent diabetes in patients with impaired glucose tolerance.

Low ankle-brachial index may be a risk factor for stroke in older patients

Abbott RD, Rodriguez BL, Petrovitch H, et al. Ankle-brachial blood pressure in elderly men and the risk of stroke: The Honolulu Heart Program. J Clin Epidemiol 2001; 54(Oct.):973-8.

A low ankle-brachial blood pressure index (ABI) is associated with an increased risk of stroke in older patients, according to researchers from Hawaii. They said although low ABI (<0.9) has been shown to be a risk factor for total mortality, cardiovascular mortality, cardiovascular disease, peripheral artery disease, and heart failure, a relationship between low ABI and stroke risk in older persons has not been identified.

To determine this relationship, researchers evaluated data from 2,767 men of Japanese ancestry participating in the Honolulu Heart Program. The men received complete physical examinations when they entered the study between 1965 and 1968 at ages 45 to 68. ABI measurements were taken for the first time during repeat examinations given between 1991 and 1993 when they were age 71 to 93. For these follow-ups, men were excluded from the study if they had a diagnosis of stroke or coronary heart disease or if they had undergone vascular surgery of the abdomen or lower extremities. Subjects were followed for 3 to 6 years for fatal or nonfatal thromboembolic and hemorrhagic stroke.

ABI was determined using systolic blood pressure measurements taken from the right arm and each ankle. The means of the two measurements were used to calculate the ABI as a ratio of the ankle measurement divided by the arm measurement. Researchers used the minimum of the two values as the ABI. They compared men with ABI <0.9 and men with ABI ≥0.9.

Researchers found that 322 men (11.6%) had an ABI <0.9. Overall, 6.0% of men with an ABI <0.9 had a stroke versus 2.9% of men with an ABI ≥0.9 ($p<0.01$). Thromboembolic events occurred in 4.6% of men with an ABI <0.9 and in 2.0% of men with an ABI ≥0.9 ($p<0.01$). Although not statistically significant, hemorrhagic stroke occurred in 1.9% of men with an ABI <0.9 compared with 0.8% of men with an ABI ≥0.9.

The authors conclude that if other studies can confirm their findings, measurement of ABI in the primary care setting may be important for assessing stroke risk in older adults.

Geriatrics®

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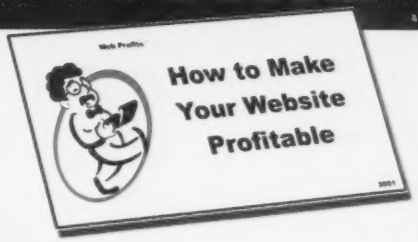

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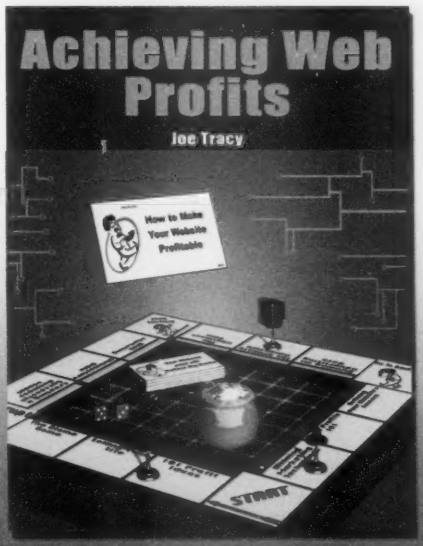

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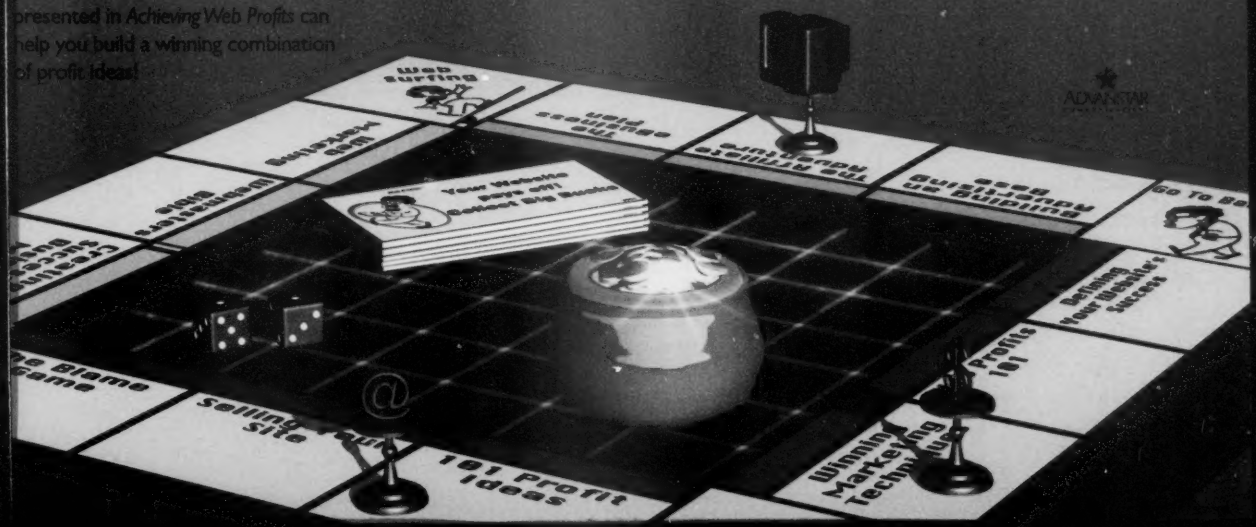

MEDICARE MATTERS

Don't overcharge patients for routine venipuncture

Don Self

Question

As a physician, which code should I use when I perform a blood draw? Is G0001 the only code I can use for Medicare patients? Is there a code that provides additional reimbursement?

Code **36410** is used for venipuncture that requires the skills of a physician (eg, patient with collapsed veins), and it generally pays about four times higher than the reimbursement for code **G0001**. Do not use this code for simple blood draws, however, because these procedures can be performed by other health professionals and do not require the skills of a physician. If you must use the higher-level code, your documentation or progress notes should explain and support the medical necessity for using code **36410** instead of **G0001**. Using the higher-level code too often could get you into trouble with Medicare.

Another reader wants to know why Medicare denies claims for finger sticks and venipuncture blood draws when code **36415** is listed on the claim form. The answer is that Medicare never pays for finger sticks, heel sticks, or code **36415**. Medicare only reimburses for the venipuncture codes mentioned above.

Question

I learned at a recent seminar to collect copayments from patients prior to showing them into examination rooms. Can this policy apply to Medicare patients? If so, do I collect a flat rate and then refund the difference after the visit?

Medicare copays are 20% of the amount Medicare allows doctors to charge for individual services. Because you do not know before the visit which service the physician will perform, you cannot collect the copayment from a Medicare patient until after the visit. For non-Medicare patients, however, you should collect copayments before showing them into exam rooms.

Question

A billing consultant told me that I can bill for a consultation and an office visit on the same day for the same patient if I address two different problems during the visit. Is that true?

No. If you only provide one evaluation and management (E&M) service, you cannot divide it into two different E&M charges. It is considered fraudulent billing.

Question

If I perform a consultation on a patient who is under observation, which place-of-service code should I use on the claim form? The patient is neither an inpatient nor an outpatient.

Patients who are under observation are considered outpatients because they have not been admitted to the hospital under "inpatient" status. The correct place-of-service code is 22.

Question

I was told that if a patient has been seen in my practice within the last 3 years, I cannot treat him as a new patient or perform a consult, even if he was referred to me by another doctor. Is that true?

Not entirely. It is true that the patient is not considered a new patient if you had a face-to-face encounter with him in the last 3 years. Patient consults, however, are not limited by this 3-year rule and are not dependent on the new or established status of the patient. You can perform a consult on a patient today and perform one on the same patient at the request of another physician next week.

Send Medicare-related questions to Don Self c/o *Geriatrics*, 7500 Old Oak Blvd., Cleveland, OH 44130 (toll-free fax 800-788-7188, e-mail **donself@donself.com**). All questions will receive a personal answer, and some will be published. No fee is charged for single questions; a consultation fee may be charged for multiple questions. Access to related information is available on the web at: http://www.donself.com/doc.html. The information in this column is designed to be authoritative. The publisher is not engaged in rendering medical or legal advice.

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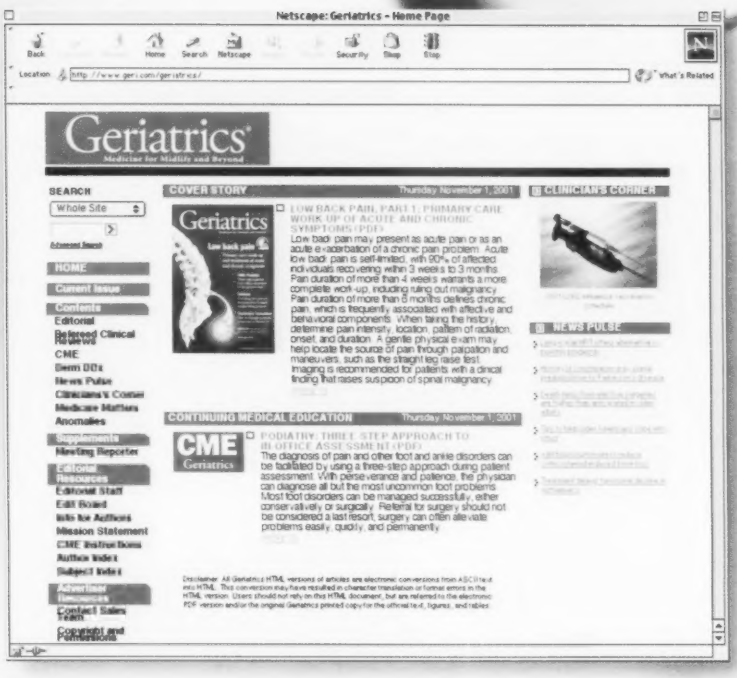

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